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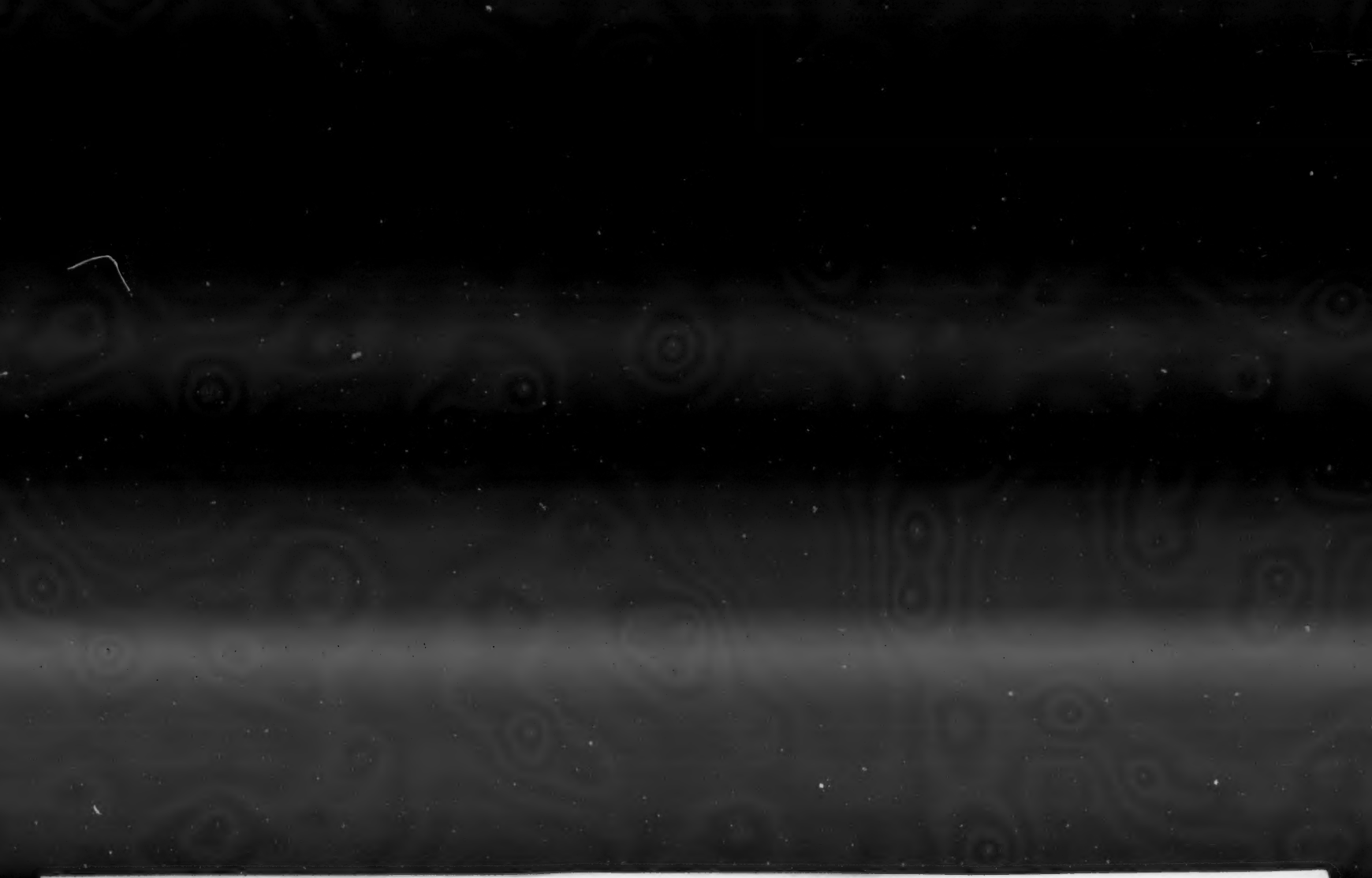

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Proceedings of the Royal Society of Medicine Vol. 44 1

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[*June* 3, 1950]

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MEETING HELD AT THE CHILDREN'S HOSPITAL, SHEFFIELD

The Delay in the Diagnosis of Tuberculous Meningitis and its Relation to the Results of Treatment

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INTRODUCTION

IT is now well established that excellent results can be obtained in the treatment of tuberculous meningitis if treatment begins at an early stage of the disease. The proportion of advanced cases, however, is high in every published series, owing to delayed diagnosis.

This delay may be due to failure to seek medical advice after the onset of symptoms, failure by the family doctor to recognise the nature and seriousness of the disease and failure of the hospital staff to take appropriate and urgent steps to establish a definite diagnosis upon which correct and immediate treatment may be based.

MATERIAL

This investigation is an attempt to find out what this delay is, where it occurs, what are its consequences and how best it can be avoided. It is based on the history and progress of 87 children suffering from tuberculous meningitis, admitted since January 1, 1948—several months after streptomycin became available for treatment, and 15 others who developed meningitis under our own eyes. Six of the latter were under observation for primary tuberculosis and 9 under treatment for miliary tuberculosis at that time (Table I).

TABLE I.—DELAY IN DIAGNOSIS

Admitted with meningitis		87
Onset known	77	
Onset not known	10	
Developed meningitis under observation ..		15
For primary	6	
For miliary	9	
Total		102

TABLE II.—ORIGIN AND LENGTH OF DELAY

Origin	Number of cases	Average no. days
First symptom to admission	77	12·9
First symptom to doctor's call	68	3·3
Doctor's call to admission ..	67	8·3
First hospital to Sheffield Children's Hospital ..	45	2·4
Admission to Sheffield Children's Hospital to treatment	66	1·2
First symptom to treatment	66	14·2

In some of the 87 cases there was considerable difficulty in determining the exact onset of the meningitis, especially when it followed miliary tuberculosis and 10 had to be excluded altogether for this reason. In the remaining 77 children the time interval between the onset of *meningitic* symptoms to admission to us varied from 1 to 28 days, with an average of 12·9 days (Table II).

The Length and Origin of the Delay in Diagnosis

The first delay occurred between the onset of symptoms and the doctor's visit. This interval is known in 68 of our cases. As some parents did not ask for help until their child became unconscious, the average delay to the doctor's first call was 3·3 days. It is noteworthy, however, that in fully one-third of the cases the doctor was called on the first day of the symptoms and in two-thirds within 3 days. Perhaps the mothers' instinct was sensitive to impending danger when to doctors the symptoms appeared trivial.

The second delay, the interval from the doctor's first call to the child's admission to hospital, is known in 67 cases and the average was 8·3 days—the longest of the various stages. In contrast to the previous stage, the doctor referred the child to hospital on the day of the first visit only once—an unconscious boy following convulsions. In one-third of the cases admission to hospital was not requested for ten days or more. Even in children of known tuberculous households tuberculosis was rarely thought of and the children's tuberculin reactions were practically never known. For example, the symptoms of a baby of a tuberculous father were attributed to simple teething at first and even when a squint appeared and convulsions started this diagnosis was maintained. After several days of unconsciousness bronchopneumonia was suspected but the baby was moribund before she reached hospital. An early diagnosis would have been possible by examination of her fundi which would have disclosed large choroidal tubercles near the disc.

An unspecified but substantial proportion of children received chemotherapy at home, without a diagnosis. This is hardly surprising, but there was a smaller, yet very important group, in which meningitis was diagnosed on clinical grounds and treatment was given at home and occasionally even in hospital with penicillin and sulphonamides, without examination of the cerebrospinal fluid. This is a particularly tragic form of mismanagement and in some cases consultants share the blame for it, having advised this course or acquiesced in its continuation.

Forty-five children were transferred to us from other hospitals. The average delay caused by this necessary transfer was 2·4 days. Some of the delay at this stage was due to our failure to provide a bed immediately, partly because of the difficulty of finding an empty bed and partly because of imperfect appreciation of the urgency of the situation in the earlier years of this review. The delay at the transferring end was often due to desire to send only established cases. It would be preferable to send unconfirmed cases, if this led to saving of time. However it is possible to record an apparent reduction in the delay at this stage from 3 days in 1948 to 1·4 days in 1950. There is need for further improvement.

The last delay occurred between the child's admission to us and the beginning of treatment. 11 children admitted in 1948 were not treated because of shortage of streptomycin. Their clinical condition and the delays at various stages of their progress were almost identical with those of the whole group, and their omission at this point would not affect the findings. The average delay in instituting treatment in the remaining 66 cases was 1·2 days with a range of 0–5 days. Some of this delay was due to slowness in completing the essential investigations. Occasionally there were genuine diagnostic difficulties leading to several days of delay.

Altogether, in the 66 treated cases, the total average delay from the first symptom to the beginning of treatment was 14·2 days. Analysis of our own untreated cases confirms the generally accepted average duration of the disease to a fatal termination as 21 days. It will be seen, therefore, that this average delay of 14·2 days corresponds to two-thirds of the symptomatic part of the disease and gives some idea about the odds against which any drug treatment must contend.

The Consequences of Delay in Diagnosis and Results of Treatment

It is generally agreed that the clinical condition of the patient is of more prognostic significance than the length of the history. For this reason apprehension was felt on starting this analysis that the final figures may not support the plea for speed in diagnosis.

In considering the results of treatment in relation to the delay in diagnosis all 54 cases have been analysed who have been treated in the Streptomycin Unit of the Department of Child Health, provided that the delay was known and that they were followed for a minimum of six months. Since streptomycin was made more freely available twenty-one months ago, not a single case was refused admission and treatment, however moribund and however long the distance.

Forty children were admitted with existing meningitis (Table III). These were divided into two groups, according to whether the delay to the first streptomycin injection was more or less than the average of 14·2 days. In the 17 cases in which treatment was begun on or after the fifteenth day, the mortality was 88·2%. In the 23 cases in which treatment was

TABLE III.—RESULTS OF TREATMENT IN RELATION TO LENGTH OF DELAY

	Delay days	No. of cases	No. of deaths	Mortality %
Admitted with meningitis	15 and more	17	15	88·2
	14 and less	23	11	47·8
Developed meningitis while under treatment for				
(*a*) primary	—	5	0	14·2
(*b*) miliary	—	9	2	
All cases	—	54	28	51·8

started on or before the 14th day, the mortality was only 47·8%. The other 14 children developed meningitis while under our own observation or treatment for primary and miliary tuberculosis. There was no measurable delay in instituting treatment in these, and only 2 of them, or 14·2%, died.

Tables IV and V show that the reduction in the mortality in the groups with shorter delay to the beginning of treatment was not due to other factors. It is seen that the largest proportion of children with miliary tuberculosis and under 2 years of age were in the group with the most favourable results. Thus the prognosis was better when there was no delay in spite of the high proportion of children in whom the prognosis would be poor because of the presence of these other factors which are generally regarded as of serious significance.

TABLE IV.—NUMBER OF CHILDREN UNDER 2 ACCORDING TO DELAY IN TREATMENT

Group	No. of cases	Under 2 No.	Under 2 %	Mortality % of group
I	17	2	11·8	88·2
II	23	10	43	47·8
III	14	8	57	14·2
All	54	20	37	51·8

TABLE V.—INCIDENCE OF MILIARY TUBERCULOSIS ACCORDING TO DELAY IN TREATMENT

Group	No. of cases	With miliary No.	With miliary %	Mortality % of group
I	17	7	41	88·2
II	23	10	43	47·8
III	14	11*	78	14·2
All ..	54	28	52	51·8

*2 of the primary cases developed miliary tuberculosis.

Taking all the 54 cases, the total overall mortality was 51·8% and the 26 survivors have been followed for an average of 16·3 months from the beginning of treatment. These figures give convincing proof that streptomycin is an effective weapon if given a chance and that earlier diagnosis is essential.

CONCLUSIONS

The first necessity to achieve earlier diagnosis is an efficient tuberculosis service, which should detect the tuberculin conversion of any child in contact with pulmonary tuberculosis at an early moment. These children should be carefully supervised for a long time, and in the first six months at frequent intervals. If a child is found to be tuberculin positive at the first examination, the infection should be presumed to be a fresh one and managed accordingly. The parents and the family doctor should be informed that the child is tuberculin positive and the significance of this finding should be explained. In this way parents might bring their children early to a doctor. Even trivial symptoms should be viewed in a different light if a child were known to be tuberculin positive.

The longest delay occurred after the family doctor had been consulted and there was no improvement in three successive years. There was nothing peculiar in the symptoms of most of these children and the description of the disease can be found in textbooks. There is need to think more often and more readily of tuberculosis, which is common enough to kill 2,000 English children yearly. There are few investigations that family doctors or welfare officers have facilities to perform on their own but the tuberculin reaction is one of them. The jelly test is simple and requires no sterilization of instruments, but few make use of this valuable test at present. If we always remember the possibility of tuberculosis and obtain the child's tuberculin reaction early on, we shall lessen the delay before sending the child to hospital.

On arrival in hospital of a child suspected of meningitis, one doctor should take the history while another performs a lumbar puncture. While the specimen is being examined, a radiograph of the chest is taken, a Mantoux reaction performed, the fundi are dilated and searched for choroidal tubercles. With this method it should rarely be necessary to delay treatment beyond a few hours.

Plastic Operation for Hydronephrosis

By J. C. ANDERSON, F.R.C.S., and WILFRED HYNES, F.R.C.S.

From the Urological and Plastic Departments of the United Sheffield Hospitals

Mr. J. C. Anderson: If we exclude cases of urethral stricture and prostatic obstruction, most cases of obstruction and dilatation of the urinary passages are due to a neuromuscular factor or a congenital anomaly.

The majority of these interesting urological cases were referred to me by my medical colleagues. Many presented with recurrent urinary infections. Only a few had other urinary symptoms, such as renal colic, and many had no urinary symptoms whatever. These frequently had a history of vague abdominal pain, sometimes in one or other iliac fossa. Dyspepsia and recurrent attacks of vomiting were quite common features. In my opinion all children with abdominal pain which cannot be attributed to a definite clinical source should be subjected to full urinary investigation. It is also worth mentioning that many adults with hydronephrosis have a dyspeptic syndrome with no urinary symptoms and a urinary investigation is called for in many such cases.

Mr. Anderson drew attention to an X-ray film taken ten minutes after the instillation of the opaque medium and withdrawal of the ureteric catheter in retrograde pyelography. Gross retention indicates a pathological degree of obstruction and the site of obstruction is accurately localized by the abrupt termination of the shadow. He showed films from the following illustrative cases:

(1) From a girl aged 10 with a three months' history of left iliac pain and general failure of health, but no urinary symptoms. Her urine was infected. Investigation showed left-sided hydronephrosis, which at operation was found to be due to obstruction at the upper end of the ureter by a leash of vessels passing to the lower pole of the kidney. This condition was relieved by the plastic operation described by Mr. Hynes. The urinary infection has not recurred.

(2) From a boy aged 6½ years. His only symptom was frequently recurring attacks of vomiting. He had no pain, no urinary symptoms and his urine was uninfected. At operation the obstruction did not appear to be due to a mechanical factor but to a persistent state of spasm at the pelvi-ureteric junction.

(3) From a boy aged 12 with recurrent attacks of left renal colic. Investigation showed persistent spasm at the pelvi-ureteric junction but no dilatation. The pelvi-ureteric junction was resected and the patient's symptoms relieved.

(4) From a girl aged 10 years with right iliac pain which was thought to be due to appendicitis. Her urine was infected and the condition was ultimately diagnosed pre-operatively as being due to a retrocaval ureter. Her symptoms were completely relieved by a plastic procedure, the ureter being detached through the renal pelvis, withdrawn from behind the vena cava and re-anastomosed by the technique to be described.

(5) From a girl aged 10 years with a history of right iliac pain. She was found to have double renal pelves and ureters which joined in the region of the right sacro-iliac joint. The ten minutes' emptying film showed the obstruction to be at the point where the ureters joined. He believed that the obstruction in such cases is due to a peristaltic wave in one element meeting a phase of spasm in the other element, this leading to stagnation, infection and dilatation. These observations were confirmed at operation and the presence of a mechanical stricture was excluded by ureteric catheterization at the operation.

(6) From a child aged 2½ years who had been operated upon for a meningocele in infancy. She now had gross distension of the bladder with overflow incontinence and infection. Her bladder was grossly trabeculated, the lesion being due to spasm at the bladder neck comparable with that found in cases of paraplegia or spinal injury. Temporary but definite relief was achieved by an injection of a local anæsthetic into the sacral canal.

(7, 8) Two cases of obstruction due to valve formation in the posterior urethra and consequent dilatation of the upper urinary tract were mentioned.

Mr. W. Hynes: Conservative operations for hydronephrosis have a bad reputation. 20% come to nephrectomy and a large proportion of the rest show persistent renal infection. There are two main reasons for these poor results:

(*a*) *Faulty operative technique.*—The chief fault is that, after re-implantation of the ureter into the pelvis, the stoma is surrounded by a circular circumferential scar which, as it contracts once more, obstructs the renal pelvis.

(*b*) *Faulty diagnosis of the exact site of the obstruction.*—Even at operation it can be very difficult to locate the exact site of the obstruction which may be in the upper ureter rather than at the uretero-pelvic junction. It is possible, therefore, to leave the pelvis permanently obstructed after an apparently successful plastic operation at the uretero-pelvic junction.

Fig. 1 illustrates the method we are using. The upper 3/4 in. of the ureter, the uretero-pelvic junction and the redundant upper pelvis are resected in one piece (B). The lowest part of the pelvis is retained and turned down as a flap (A). The upper two-thirds of the opening thus created in the renal pelvis is closed with a continuous plain 4/0 catgut suture. The

upper ureter (C) is then slit downwards for 1 in. (a) and its edges anastomosed to the edges of the aperture in the lower third of the pelvis and to the edges of the pelvic flap—also by a continuous plain 4/0 catgut suture. The renal pelvis is drained for a few days by a nephrostomy but the anastomosis is not splinted by an indwelling ureteric catheter.

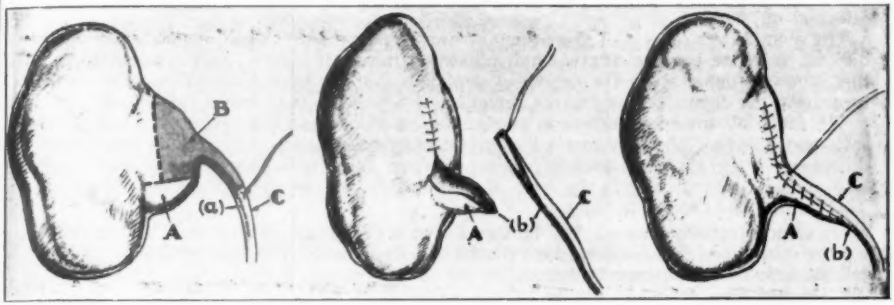

FIG. 1.—Steps in the plastic repair of hydronephrosis. (From "Retrocaval Ureter", ANDERSON, J. C., and HYNES, W. (1949) *Brit. J. Urol.*, **21**, 209. Messrs. E. & S. Livingstone, Edinburgh.)

This operation ensures: (i) Dependent drainage of the renal pelvis. (ii) That the new pelvis drains into the ureter that has scar tissue at only one point of its circumference (b, Fig. 1). Subsequent contraction cannot, therefore, narrow the lumen of the ureter at this point. (iii) By radically resecting the whole uretero-pelvic region together with the upper end of the ureter we ensure that the obstruction is removed and is not left behind to obstruct the new renal pelvis.

Parenteral Alimentation in Relation to Nitrogen Balance and Liver Damage

By S. A. DOXIADIS, M.D.

Senior Lecturer in Child Health, University of Sheffield

THIS discussion concerns the parenteral administration of nitrogen in the form of protein and its derivatives. Most workers when giving nitrogen parenterally in any form aim at attaining a positive nitrogen balance. Recent advances in liver pathology have added a second aim: the prevention of liver damage. The problem will therefore be examined under two headings: (1) The attainment of nitrogen equilibrium or of a positive nitrogen balance; (2) The prevention of liver damage.

(1) NITROGEN BALANCE

After the first day of restriction a normal adult, deprived of food, derives approximately 13% of the calories he needs from tissue protein (Cuthbertson, 1948). Gamble's team (Gamble, 1947) working on the "life raft ration" showed that this nitrogen loss is halved if 100 grammes of dextrose are given daily. On this intake about 40 grammes of tissue protein are catabolized every day. If the same amount of animal protein (egg) is added to the daily intake of dextrose, the nitrogen loss is only insignificantly reduced, because the ingested protein is used for energy purposes and not for protein anabolism. Gamble (1947) has further quoted unpublished data of Schwimmer and his team according to which only when 60–70% of the calorie requirements are provided from other sources is nitrogen equilibrium approached on an intake of 40 grammes of protein daily.

It is true that some workers (Elman *et al.*, 1945; Elman, 1947; Werner, 1948) claim that they achieved a positive nitrogen balance by giving very large amounts of nitrogen, although the total calorie intake was low. But even if their reports are confirmed by others the amount of nitrogen which has to be given is such as to make it impracticable for parenteral use. All these observations refer to normal subjects.

It must be remembered, however, that injury and disease, apart from possibly interfering with the intake of protein, increase protein catabolism and therefore adversely affect the

nitrogen balance (Peters, 1948). Werner (1947) suggested that the negative nitrogen balance following injury and disease can be explained on the basis of inadequate nitrogen intake without postulating an increased protein catabolism. This awaits confirmation.

On the other hand protein-depleted animals use nitrogen more economically, requiring less nitrogen for the attainment of equilibrium. Furthermore there is less protein destruction following injury or disease in the protein-depleted subject than in others (Allison, 1948; Silber *et al.*, 1946).

The quantitative aspects of this saving of nitrogen by the previously depleted patient are difficult to define because of great individual variations. It is likely that the magnitude of this economy depends on the degree of depletion, but we have no accurate criterion for measuring the degree of the protein depletion of a patient (Homburger, 1948).

The materials used for parenteral administration of nitrogen are various casein hydrolysates and plasma. The only casein hydrolysate available in this country is Casydrol, which differs very little from the American product Amigen. Casydrol is an enzymic digest of casein, 60% of the nitrogen being in the form of amino acids and the rest in the form of peptides. The limitations of this material are:

(1) Concentrations above 2·5% damage the vein (Williams, Bishop and Young, 1949). On the other hand American workers (Dodd and Rapoport, 1946) have used 5% Amigen in infants without any untoward effects.

(2) Rapid infusion causes nausea and vomiting.

(3) The pH is low (6·5 according to the manufacturers).

When examining the effect of Casydrol on nitrogen metabolism the first consideration is that some of the nitrogen given is lost in the urine directly, without taking part in any metabolic process (Allen *et al.*, 1950; Elman, 1948; Smyth *et al.*, 1947). As this lost nitrogen is mainly in the form of peptides (Eckhardt *et al.*, 1948; Christensen *et al.*, 1946) the higher the peptide content of the hydrolysate the greater the loss. Expressed otherwise, the less complete the hydrolysis the less nitrogen will remain available for metabolic purposes. The remaining peptides and amino acids are used either to provide energy or for tissue building, depending on the number of calories simultaneously provided from other sources.

Most workers agree that approximately two-thirds of the total calorie requirement must be found from other sources before amino acids can be spared as building materials. This means giving 60–70 calories per kg. of body-weight to infants and about 40 to children. At present, the only other source of calories in parenteral alimentation is dextrose. The amount required to supply 60 calories would be either 150 ml. of a 10% solution or 300 ml. of a 5% solution of dextrose. Both methods are impracticable, the former because of the risk of thrombosis of the vein, the latter because of the excessive amount of fluid. There is so little information available about the nitrogen balance of infants and children while on parenteral alimentation that it is not possible to say whether the above considerations derived from work on adults apply equally to infants and children. Reference is frequently made to the work of Shohl (1943). Positive nitrogen balance was achieved by him in 19 of 20 infants on parenteral intake. Valuable though this work is, it was done at a time when we lacked our present knowledge of the interdependence of total calorie and nitrogen intake and of the significance of previous protein depletion. These data are not to be found in Shohl's paper and it is therefore impossible to draw any further conclusions. For the same reasons the work of Jonxis (1946) is not helpful.

The difficulty, therefore, is not how to give enough amino acids parenterally, but how to give enough calories, from whatever source, so that amino acids can be spared for the purpose for which they are given.

Extensive work has been done in recent years on the intravenous administration of fat. One of the preparations used without any untoward effects contained 160 calories per 100 ml. (Mann *et al.*, 1949; Gorens *et al.*, 1949) while 100 ml. of 2·5% Casydrol in 5% dextrose only supply 30 calories. If only one-third of the total fluid intake consisted of this preparation of fat and two-thirds of the dextrose-amino acid solution the calorie intake would be 80 cal. per kg., a very satisfactory figure.

The second preparation which has been extensively tried recently is an acid digest of casein, called VUJN (Eckhardt and Davidson, 1948), which is not yet available in this country, but as it offers definite advantages over the enzymic digest, the main differences from Casydrol are presented.

(1) There is no nausea or vomiting even with rapid infusion (Elman, 1948; Parson *et al.*, 1950; Smyth *et al.*, 1947).

(2) It has been given to adults in concentrations up to 10% without damage to the veins (Parson *et al.*, 1950). Work on infants has not yet been published, but it is fair to assume that a concentration of at least 5% will be well tolerated.

(3) Hydrolysis is nearly complete and approximately 82% of the nitrogen is in amino acid

form (Eckhardt and Davidson, 1948). In view of what has been said before on the immediate nitrogen loss in the urine this is a definite advantage.

(4) Methionine (d.l.), tryptophane (d.l.) and glycine have been added to this preparation.

The remaining method of giving nitrogen parenterally is infusion of plasma. The main limitations and disadvantages of plasma are as follows:

(1) It is only available in limited quantities.

(2) Danger of "serum hepatitis" especially when pooled plasma is used.

(3) Expansion of intravascular compartment (osmotic effect of protein). This is not a serious limitation if the plasma is given slowly through a continuous drip.

(4) Expansion of extracellular compartment, mainly due to the high sodium content. This is the main limiting factor in infants and a preparation of a plasma with low sodium content would be valuable.

When nitrogen is given parenterally as whole protein, a striking difference is seen in nitrogen balance (Allen *et al.*, 1950; Kremen, 1947; Moore, 1949; Werner, 1948). Nitrogen is retained in the body, much better than when hydrolysates or amino acids are given. This is due to two factors:

(1) There is no loss in the urine.

(2) The whole protein is broken down very slowly to the constituent amino acids. As long as it is in protein form it cannot be used for metabolic purposes and it is not therefore excreted.

There is therefore a positive nitrogen balance, but it can be claimed that it is purely artificial, since it means not that new tissue proteins are being built, but that nitrogen is retained in a metabolically inert form. Whether this is true or not obviously depends on what happens to this protein between the time it is injected into the circulation and the time it is finally broken down into amino acids. If repeated injections are given, as much as 25%–45% of the total amount may be retained in the circulation and increase the volume of the plasma proteins (Eckhardt *et al.*, 1948). A small part of the rest is slowly broken down, but the fate of the largest part is still uncertain.

Whipple and his school (Whipple and Madden, 1944; Terry *et al.*, 1948), believing that proteins can enter and leave cells without first being broken down to amino acids, maintain that the amount of protein not retained in the circulation has entered certain body cells, while Eckhardt and his team (1948) think that it is to be found in the lymphatic system. Both theories have points in their favour, but if Whipple is right then this part of proteins, far from being inert, is extremely valuable, because it by-passes the energy pool.

More certainty exists regarding the rate at which this protein is eventually broken down to amino acids. It has been found (Eckhardt *et al.*, 1948) that, five days after injection, 50% of the proteins have been broken down and 50% are still intact. In other words the half-life of the injected protein is five days. When plasma is given every day the amount of amino acids released increases progressively. If the same amount of plasma is injected daily, it is possible, by using the decay equation (Eckhardt *et al.*, 1948), to estimate the amount of protein which is broken down every day into its constituent amino acids. On the fifth day of the injections, for instance, the amino acids released correspond to 50% of the daily dose of protein and on the tenth day to 75%. This slow release may be a disadvantage, but it minimizes the loss of amino acids in the urine. In addition to this there is a pool of proteins which, when further injections are stopped, is slowly broken down to amino acids over a number of days. This supply of amino acids may be very useful if the plasma transfusions have to be stopped for technical reasons before the intake by mouth has returned to normal.

Once the amino acids are free they have the same fate as any other amino acids injected as such. They may be used to provide energy if sufficient calories are not available from other sources, and if energy requirements are otherwise met the amino acids will be used as building materials.

(2) Prevention of Liver Damage

The finding of a fatty liver in infants and children dying after a long illness involving some degree of undernutrition is well known. It is now accepted that the fatty infiltration of the liver is the precursor of a diffuse hepatic fibrosis and that it is a reversible process, responding to lipotropic factors (Himsworth, 1947). But although fatty infiltration of the liver is a great handicap it does not seem to be the immediate cause of death. The lesion with which we are concerned in planning emergency treatment is an acute or massive necrosis which is usually fatal and which may develop on a fatty or on a healthy liver. We know much less about it than about fatty infiltration. The lesions described by Bonham-Carter (1947) as miliary necrosis are possibly the same thing. This condition has been very well studied in animals (Himsworth, 1947). When rats are put on a diet conducive to necrosis, they show no change for many days but then they develop an illness and die within a short time, sometimes a few hours. It has been shown that the nutritional factor, the absence of which leads to hepatic necrosis, is cystine.

Some infants, dying after a period of deficient nutrition, show clinical and histological similarities to these cystine-depleted rats. The clinical picture is as follows:

A child has a prolonged illness, usually gastro-enteritis during which the main alimentation is parenteral. There seems to be some improvement, and oral feedings are resumed, but before the oral intake is back to normal, the infant quite unexpectedly develops œdema, a large liver, perhaps jaundice, and dies within a few hours or days. Investigation of his intake in the two to three weeks preceding death shows that although water, salt and glucose had been given in adequate quantities the protein intake was small. This is not the picture of fatty infiltration. It appears to develop in a fairly short space of time and the critical period is probably the two weeks before death. Schlesinger, Payne and Burnard (1949) did not think that fatty infiltration alone can explain the whole clinical picture.

The following are two illustrative case histories.

Case I.—A 6-months-old female infant was treated for gastro-enteritis and was discharged apparently well. One week after discharge there was a relapse and the infant was readmitted a week later very ill and dehydrated. The intake of fluid, calories and protein from the first day of the second admission till death, is presented in Fig. 1. It should be noted that salt intake (sodium, chloride, potassium and calcium), although not shown in Fig. 1, was adequate. Calories were given mainly in the form of dextrose. There was clinical improvement on the twelfth day after admission, so oral feeding was resumed the following day. One day later, while the clinical improvement continued and the impression was gained that progress would be satisfactory, œdema developed, a large liver was found and the infant died within a few hours. It can be seen that there was practically no protein intake for a fortnight and perhaps longer. The protein intake from the fifth to the eighth day after admission is rather theoretical, since at that time there was persistent vomiting and diarrhœa. The histological picture of the liver is shown in Fig. 4.

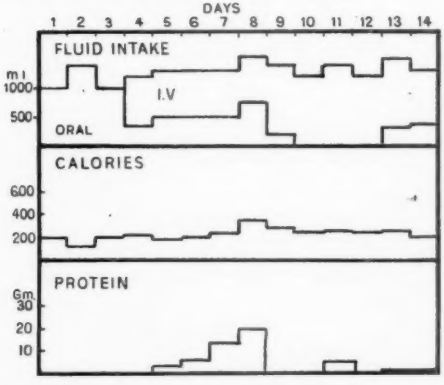

FIG. 1 (*Case I*).—Intake of fluid, calories and protein from first day of the second admission until death.

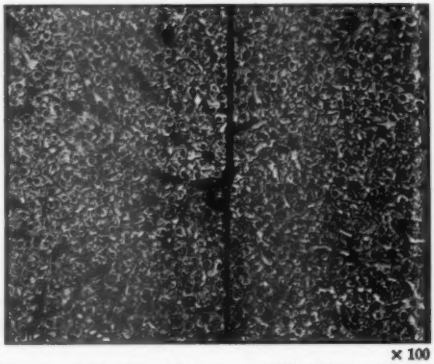

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FIG. 4.—Liver from Case I. A child dying suddenly from protein-deficient feeding.

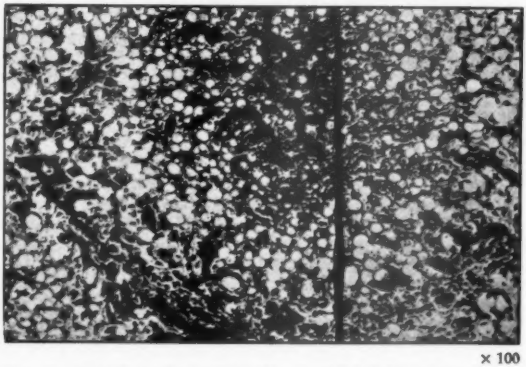

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FIG. 9.—The liver from Case II. A child dying several days after the onset of liver failure.

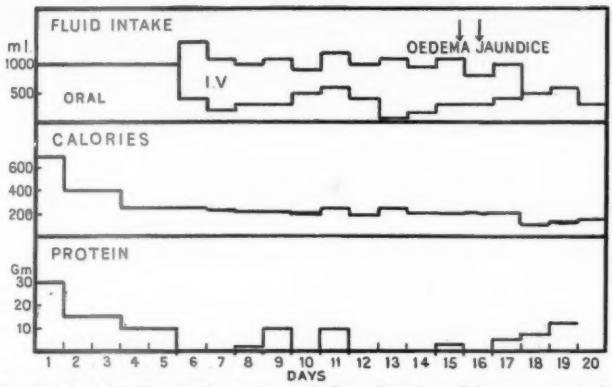

FIG. 2 (*Case II*).—Intake of fluid, calories and protein from first day of the gastro-enteritis until death.

Case II.—A 7-months-old male infant was treated for otitis media and when this got better and he was ready for discharge he developed gastro-enteritis. Fig. 2 presents his fluid, calorie and protein intake from the first day of the gastro-enteritis until death. As in Case I salt intake was adequate and the calories were mainly in the form of dextrose. On the thirteenth and fourteenth days of the gastro-enteritis there was again the impression that the infant was improving but œdema and a large liver developed on the fifteenth day and jaundice appeared twelve hours later. These persisted and death occurred four days later. In this case also, protein intake for the two weeks before death was minimal. The histological picture of the liver is shown in Fig. 9.

Apart from cases of poisoning, whenever the lesions of massive necrosis have been found in man, the pathogenesis has not been as clear as in experiments. Toxic and infective agents, as well as nutritional deficiencies, have been held responsible and the ætiology is therefore uncertain. Fortunately, when it comes to prophylaxis, the issue is simpler, because independently of the nature of the primary noxious agent, the absence of certain factors from the diet makes both animals and man much more liable to severe liver damage (Himsworth, 1947). The factor concerned in rats is cystine. The significance of tocopherol has been recently discussed by Himsworth (1949). It is not known whether it is the same in man. If we assume that it is, we have to estimate the content of both cystine and methionine in the various materials used for parenteral administration of nitrogen, because cystine can be formed in the body from methionine. These data are presented in Table I. For as long as

TABLE I.—CYSTINE AND METHIONINE CONTENT OF PLASMA, CASYDROL AND VUJN

	Per 100 ml.	Per max. allowed volume/kg. body-weight ml./kg.	Cystine and methionine
Plasma	0·4 gramme	50	0·2 gramme
Casydrol 2·5% ..	0·09 gramme	150	0·135 gramme
VUJN 5%.. ..	0·32 gramme	150	0·48 gramme

[Data from Block and Bolling (1945) and Eckhardt and Davidson (1948)]

sodium-free plasma is not available, only 50 ml. of plasma per kg. of body-weight per twenty-four hours can be considered as a safe dose, especially in infants, while up to 150 ml. of Casydrol or of VUJN may be given per kg. of body-weight in twenty-four hours.

It can be seen that VUJN provides more amino acids than the other preparations, though part of the methionine added to VUJN is in d-form and therefore metabolically inert. Allowance also has to be made for an immediate small loss in the urine. With Casydrol this loss is greater for the reasons already mentioned.

When plasma is used the slow release of amino acids may be a disadvantage. Even if Whipple's theory is correct that proteins may enter and leave cells, it is not known if the intact protein molecule has the same effect as the amino acids cystine and methionine.

Clinical experience has not yet answered the question whether plasma can prevent liver damage. Varco's paper (1946) is often quoted as proving that plasma and blood cannot prevent liver damage. His evidence, however, was based on 2 cases of elderly patients and is not convincing. Final conclusions are deliberately not drawn concerning parenteral administration of nitrogen and no definite recommendations are made. There are still too many unknown factors needing further investigation. All that can be said is that in planning the treatment of each individual case many factors have to be taken into consideration. In

opening this discussion an attempt has been made to present these factors and to discuss their relative importance.

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Dr. J. L. Emery (*Pathologist to Children's Hospital and Lecturer in Pathology, University of Sheffield*): It has been pointed out that the protein requirements of ill children must be considered in terms of particular amino acid needs as well as the total nitrogen intake and balance. The evidence regarding amino acid deficiency in liver failure has also been summarized.

It is well known that, following gastro-enteritis, children frequently die with liver failure. The cases presented here are designed to show to what extent the histological changes in the liver of children, dying fairly suddenly following gastro-enteritis, can be related to the lesions produced by amino acid deficiency in growing rats.

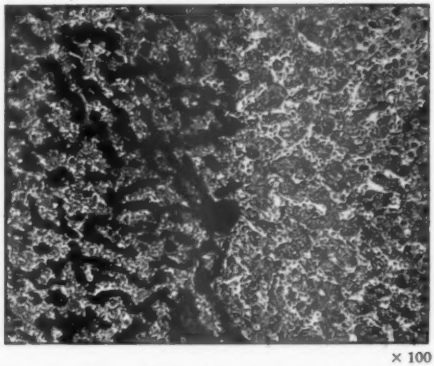

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FIG. 3.—Normal liver showing normal vascularity of the lobule.

The animals which Himsworth and others fed on a diet deficient in methionine remained apparently well for varying periods and then died rapidly with acute liver necrosis. There appear to be two factors in the production of the liver failure. The first is an alteration in the structure of the liver cell with swelling of the cell, and the second, that the swollen liver cells constrict the sinusoids within the liver lobules. This vascular constriction produces secondary changes in the cells of the lobule due to the anæmic anoxia. This mechanism can easily set up a vicious circle by the anoxia producing further swelling of the liver cell with further vascular constriction and increasing anoxia. Incidentally it must be remembered that these lesions are not produced by general starvation.

In histological preparations it is possible to obtain an idea of the extent to which this intralobular anæmia has occurred by comparing the patent blood vessels within the lobules with a normal vascular pattern. In the illustrated cases presented, the blood vessels have been blocked in on one side of the lobule only.

In the normal liver (Fig. 3) taken from a child dying rapidly with no sepsis or malnutrition, it is seen that the lobule is extremely vascular, the blood vessels taking up as great a volume as the liver cells. Compare this picture with (Fig. 4) the liver of Case I who died suddenly after being treated with a protein deficient diet for fourteen days (Fig. 1 graph); the anæmia in the lobule is obvious. The most marked instance of lobule anæmia that I have found is from a child aged 7 months who had been vomiting for a month. This infant developed a persistent acidosis and died suddenly with massive necrosis of the liver (Fig. 5).

In these cases (Figs. 4 and 5) the liver changes are those of cellular necrosis and lobule anæmia occurring in a relatively normal liver—but fatty changes are frequently coincidental in any child that has an infection for any length of time. Fatty change in the liver does not of itself appear to produce anæmia within the lobule. This is illustrated in Fig. 6. This child aged 4 months developed Sonne dysentery with bloody diarrhœa, and the general condition deteriorated steadily to death. There is obviously little normal liver parenchyma present, but the mechanism of the changes in this case is obviously different from that in Figs. 4 and 5.

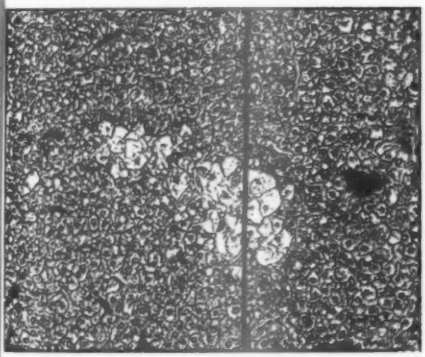

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FIG. 5.—Liver from a child dying with massive necrosis of the liver following prolonged and persistent acidosis.

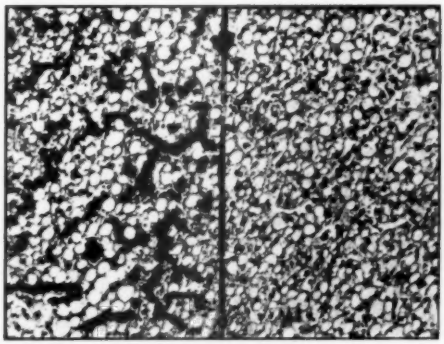

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FIG. 6.—A fatty liver showing almost normal vascularity.

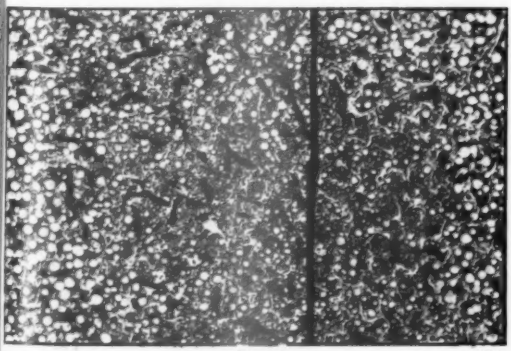

FIG. 7. × 100

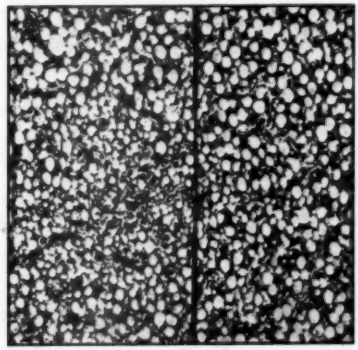

FIG. 8. × 100

FIGS. 7 and 8.—Liver showing both fatty and anoxic changes from two children dying suddenly following treatment for gastro-enteritis due to a parenteral infection.

The further cases are instances in which anæmic-anoxic changes occurred coincidental with fatty change. Fig. 7 is from a child aged 4 months who had gastro-enteritis associated with a parenteral infection. Ten days after an apparently adequate intravenous fluid treatment, the child died suddenly. Fig. 8 is from a child aged 6 months having an infection with persistent acidosis and again following an apparent adequate response to intravenous fluids, death was unexpected and rapid. Case II (Fig. 2) described above by Dr. Doxiadis was a child who developed jaundice and evidence of liver failure several days before death. The liver from this case is illustrated in Fig. 9. The liver shows what could well be a later stage of the livers shown in Figs. 4 and 7.

The liver cells at the centre of the lobules have almost disappeared while an avascular state still occurs in the mid-zone of the lobule. The changes seen in these livers are similar to those produced by amino-acid deficiency in rats. It would not, however, be justifiable to say that the children illustrated here died from the same amino-acid deficiency as do rats. But the mechanism in the production of the liver failure in the animals is sufficiently similar to the lesion in the children to suggest that some imbalance in amino-acid metabolism may well have been a major factor in the liver failure in these children. In Cases I and II it was shown that a starvation in nitrogen had occurred, and the association of this with the liver lesion is very likely, and certainly sufficiently conclusive to make the adequate administration of protein and amino acids a primary concern in the parenteral feeding of ill children.

Dr. Winifred Young: At the Queen Elizabeth Hospital for Children, Hackney, it has been found that many of the patients who require these protein preparations are infants suffering from gastro-enteritis. If they are unable to tolerate food for periods exceeding forty-eight hours, such babies receive both plasma and casein hydrolysate solution, the total amount of protein being about 1·0 gramme per lb. body-weight daily. Careful regulation of the daily intake of electrolytes to replace the losses from the bowel is essential for these patients. The need for caution in the administration of the preparation of casein hydrolysate available in this country should be appreciated. The content of sodium and potassium in successive batches has been found to vary and it is not possible to regulate the total daily intake of electrolytes unless the content of each of the solutions being given is known. It would be a great help to pædiatricians if the manufacturers of protein digests for parenteral administration would analyse each batch of the preparation for sodium and potassium and other electrolytes and state the amounts on the labels of the bottles in which it is dispensed.

Professor R. S. ILLINGWORTH showed the following film.—**Development of Locomotion.**

The following cases were shown:

Hysterical Aphonia.—Professor R. S. ILLINGWORTH.

(1) **Tuberculous Meningitis with Bulbar Palsy. Good Progress.** (2) **Neurological Syndrome Resembling Amyotonia Congenita.**—Dr. JOHN LORBER (for Professor R. S. ILLINGWORTH).

(1) **Ganglioneuroma of Spermatic Cord.** (2) **Eosinophilic Granuloma.** (3) **Cholecystitis.** (4) **Diaphragmatic Hernia.**—Mr. R. B. ZACHARY.

Dermatomyositis with Retinitis.—Dr. T. COLVER.

Idiopathic Precocious Puberty.—Dr. K. B. THORNTON (for Dr. T. COLVER).

Ehlers-Danlos Syndrome.—Dr. M. HILLS (for Dr. T. COLVER).

Refractory Anæmia with Eosinophilia.—Dr. K. B. THORNTON (for Professor E. J. WAYNE).

(1) **Amyotonia Congenita.** (2) **Paraplegic Poliomyelitis following Appendicectomy.**—Dr. C. C. HARVEY.

Flaccid Paraplegia, Dating from Birth and Due to a Local Lesion of the Cord.—Dr. D. G. H. STONE (for Professor R. S. ILLINGWORTH).

Gangrene of Toes—Cause Unknown.—Dr. M. G. PHILPOTT (for Professor R. S. ILLINGWORTH).

Generalized Scleroderma.—Dr. J. N. BRIGGS (for Professor R. S. ILLINGWORTH).

Peripheral Type of Muscular Dystrophy.—Dr. R. R. GORDON.

Hand-Schüller-Christian Disease.—Dr. J. M. GARVIE (for Professor E. J. WAYNE).

(1) **A Syndrome Comprising Dwarfism, Microcephaly with Mental Defect and Bilateral Neuropathic Keratitis.** (2) **Congenital Toxoplasmosis.** (3) **Ocular Torticollis (Two Cases).**—Mr. A. B. NUTT.

Section of Physical Medicine

President—W. YEOMAN, M.D.

[*October* 11, 1950]

DISCUSSION ON THE MANAGEMENT OF OSTEOARTHRITIS OF THE HIP-JOINT

Dr. W. S. Tegner (London): *The management of the sufferer from osteoarthritis of the hip.*—The patient suffering from osteoarthritis of the hip presents certain very definite problems to the doctor whom he consults. First, he is suffering from what is, to me at least, an incurable disease, which one can only treat by symptomatic methods. Secondly, he is usually in the older age-group and powers of adaptation to new circumstances may not be as adequate as they are in younger people. And thirdly, the patient is often otherwise fit and well and to find himself suffering from a painful and disabling local condition is often most disturbing.

The general management and instruction of the patient.—Once the diagnosis is clearly established the news must be broken to the patient that the disease from which he is suffering does not preclude good health nor lead to progressive and inevitable crippling but that, while much can be done to relieve the symptoms, resolution of the pathological processes which exist in this condition cannot be expected; in other words it is incurable. The patient must then be told that the hip is an important weight-bearing joint and that all efforts must be made to preserve its function with minimum disability. He must remain up and about; the joint must be kept as mobile as possible, but such mobility must be attained with the *minimum* of weight-bearing. Rest alone may relieve symptoms but will lead to rapid muscle wasting, and thus the patient must understand that non-weight-bearing activity, such as exercises in the lying position and cycling, are of great value in keeping up the tone of the muscles which are, to him, the props of the damaged joint. Most patients understand the logic of these statements. Again, these patients are often heavy, partly from diathesis and partly from inactivity resulting from this disease, and such patients must be instructed in what to eat and what to avoid. Fortunately most patients seem to like being put on a diet as the idea of the connexion between diet and rheumatism is firmly fixed in their minds. But, unfortunately, the components of an ideal reducing diet are the most strictly rationed and difficult to come by of all foodstuffs in England today, and it is difficult to advise the best without infringing the principles of rationing! Another difficult problem is that of occupation. When retirement on a pension is due this makes things easier, but too often the man is engaged in a heavy occupation still feeling capable of work were it not for the increasing pain in the hip. Unfortunately a change of occupation is not easily obtained: in some cases the Disabled Register is helpful.

The prescription of physiotherapy.—Active methods whereby the patient makes the effort and does the work are far more valuable than passive. Thus the first step is to inaugurate a regime of non-weight-bearing exercises. In the early stages individual instruction will be needed but the patient should join a suitable group as soon as possible. It is to the dis-

advantage of the patient in the higher economic levels that he can afford purely individual treatment and misses the fun and games of group treatment. Hydrotherapy is excellent as non-weight-bearing exercises are most easily performed in water. Exercise in the Guthrie Smith slings has proved a most valuable and effective substitute. Heat by shortwave diathermy relieves muscle spasm and pain and increases the vascularity of capsule and ligaments. It is, however, a passive form of therapy and loses most of its value if not combined with exercise. Faradism is sometimes employed in an attempt to build up the muscles which have wasted owing to spasm and disuse. But faradism is a very poor substitute for active voluntary muscle contraction and should only be used to re-educate the patient in the use of his own muscles. In the building up of adequate muscle there is no substitute for active voluntary contraction and the harder way of personal effort will achieve results where passive therapy is of little value. In my opinion massage plays no part in the management of the patient suffering from osteoarthritis of the hip.

The use of intra-articular injection has had its vogue and is still of value in selected cases. The fundamental effect is probably obtained by the use of local anæsthetic, and is not due to other substances whose intra-articular injection has been advocated. It is not always easy to enter the hip-joint but results do not seem to depend on accurate injection into the joint but rather on infiltration of the capsule and periarticular tissues. I think that successful results are obtained by anæsthetizing the painful capsule and by relieving muscle spasm and thereby allowing for a period of freer and less painful movement; during this period it is possible that a certain amount of stretching and even of breaking down of adhesions takes place. Some patients very much appreciate the period of relief of symptoms thus obtained and come back for more. Unfortunately I am unable to confirm the findings of those who claim that osteoarthritis of the hip can be "cured" by intra-articular injection, and I feel that this is another form of symptomatic treatment.

The orthopædic surgeon has naturally interested himself profoundly in osteoarthritis of the hip. The operation of vitallium mould arthroplasty has given many of my patients wonderful relief, but I believe that half the secret of success lies in the most careful and rigid selection of suitable patients.

Results of treatment exclusive of hydrotherapy and arthroplasty.—In 68 consecutive patients from my series at the London Hospital I found that as a result of general management and physiotherapy, three-quarters of these had received symptomatic relief and subjective improvement, and were in fact grateful patients; though none of them are cured.

If osteoarthritis of the hip is complicated by any other disease, general or local, the prognosis is rendered very much worse; similarly the older the patient is the less hopeful is the outlook. But my experience in a very large out-patient clinic has led me to disagree with certain time-honoured concepts about the incidence and ætiology of this disease. I agree whole-heartedly that osteoarthritis will more readily affect a hip, or any other joint, that has previously been damaged but at least half my patients could give no history of previous joint damage and the condition had apparently arisen *de novo*. At the London Hospital there was no evidence that "microtrauma" and "excessive wear and tear" or any such ætiological factor played a part. Osteoarthritis is just as likely to attack the sedentary worker as the manual labourer, a fact which was pointed out by Heine in 1926, and the severity of the symptoms depends very greatly on the affected individual. The same degree of osteoarthritis will cause severe pain and disability in one patient and minimal trouble to another. These facts need careful consideration in our long-term view of the correct management of the osteoarthritic.

All I have said about the management of the patient can be summed up as a confession of failure. One can relieve but one cannot cure. One's knowledge of the ætiology of the condition is not quite so depressing. In a certain proportion the osteoarthritis was due to previous joint damage in the treatment of which the future possibility of secondary osteoarthritis would have to be considered. The so-called idiopathic osteoarthritis, however, leads us to the hard core of the problem.

I suggest that the factors lying behind the development of primary osteoarthritis are genetic and that there is a type of joint structure which is inherited and which tends to break down under conditions of stress which would not damage joints of sounder structure. Thus the joint of poor quality will not stand up to heavy manual work as well as the joint of good quality, and the joint of poor quality will reveal its inadequacy more readily in the heavy worker than in the clerk. Compare the work of Stecher (1948) on the inheritance of Heberden's nodes.

A time will come when the medical histories of a vast number of families in this country will be on record and available to statisticians; I think then we shall find that the tendency

to develop osteoarthritis of the hip is inherited. Should my suggestion prove true that so-called idiopathic osteoarthritis occurring in one man but not in another who is subject to the same stresses, is due to the inheritance of a particular type of joint structure, we shall be then faced by the problem of how that affects those who deal with the disease. We shall have to face a major problem of preventive medicine. We shall have to guide our susceptibles into occupations which do not throw strain on the hip-joints, and I suppose, marry them into families whose joint structure has proved adequate!

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Mr. R. Broomhead (Leeds): I understand that I have been asked to this meeting of the Physical Medicine Section to show members the film of our post-operative treatment of vitallium mould arthroplasty, but it was also suggested that I should give some indications for the operation. That role, however, has been passed on to Dr. Reah and I shall summarize what we have found to be important as the result of our experience of about 200 vitallium mould arthroplasties.

The patient must be carefully selected. He must not expect the operation of itself, or the operator, to cure him. He must *want* the operation. He must understand that the post-operative interest that he himself takes in his recovery has a great bearing on the quality of his new hip. If a patient will work according to after-care instructions he may reasonably expect good movement. The physical condition of the patient need only be such that he is capable of making the necessary post-operative effort. The flabby state of the fat elderly woman militates against a good range of movement.

In my experience age does not greatly affect the quality of the result of a mould arthroplasty. As long as the patient has enough physical and mental stamina to sustain him through the after-treatment, age is no bar either to the operation or to the obtaining of a good result. It is therefore possible to contemplate the operation in patients up to the age of 70.

Quite a number of patients with osteoarthritis seem to be deaf, and it is very difficult to make them understand the necessities of post-operative treatment.

Sex appears to have no bearing on the result.

The most important local factor is the condition of the patient's muscles. The nearer the muscles approach to normal, the better the outlook.

Those patients who have wholly or mainly a mechanical cause for their disability obtain the best results.

These are (1) Congenital dislocation of hip; (2) traumatic cases; (3) osteoarthritis secondary to Perthes' disease or slipped epiphysis.

At operation, various degrees of fibrosis are found. The worst muscles are in those patients who have been allowed to become the "end-results" of rheumatoid arthritis or of ankylosing spondylitis. These patients have thin strap-like muscles; the individual fibres are much reduced in number, they are pale and do not seem to possess normal elasticity, the fibres are bound to each other by fibrous tissue; and groups of muscles and tendons are not only adherent to each other but to the capsule of the hip-joint and to the ilium.

Between the adherent rheumatoid group and the traumatic and congenital cases whose muscles are of normal quality, are the many osteoarthritic patients whose muscle state is variable. Some have fairly free muscles whilst others are adherent. I know of no criteria that can determine their state until the muscles are actually seen at operation.

The acute and subacute hip associated with rheumatoid arthritis or ankylosing spondylitis is in an ideal state for a vitallium mould arthroplasty. When relaxed under the anæsthetic they have a good range of movement, their muscles are still in relatively good condition, the joints have not undergone bony ankylosis, and the bones themselves are not sclerosed so that the operation does not make undue physical demands upon the surgeon. It is possible therefore to operate on these patients and give them a vitallium mould. By relieving them from pain they can maintain muscle control, tone, and power until the disease is quiescent, and they are left with a mobile, painless hip, in marked contrast to the stiff hip which is otherwise their lot—a hip solid and very difficult to deal with by any form of surgery. The fact that a patient with an active condition can maintain mobility of body during the acute or subacute stages, means that not only are the hip muscles kept free and active, but that the patient's general condition is better both physically and mentally throughout an illness which is apt to be long and trying.

The muscles of the acute rheumatoid are found at operation to be not adherent; they can therefore be re-educated and their power restored once the pain of movement has been eliminated by a mould arthroplasty.

Physicians should therefore send their cases early to the orthopædic surgeon so that he may have the opportunity of ensuring that the patient has a mobile painless hip.

The intra-articular condition of the joint seems to have little bearing on the result, though a joint which is the site of very extensive extra-articular osteophytes tends to be surrounded by muscles whose tendons and bellies are adherent to each other and to the hip capsule. One can expect therefore that these patients will have a more difficult and more prolonged convalescence than the average case.

A pre-existing deformity adds to the problem. There are three common deformities—those of adduction, flexion, and external rotation.

When the hip is freed by operation, the adduction deformity seems to disappear. It is a deformity which rarely causes difficulty.

A flexion contracture can often be corrected by a patient willing to work hard at stretching the flexor muscles, and the more troublesome deformity is the position of external rotation taken up by many osteoarthritics. Often it is a deformity that has been developing or present for years; it is difficult to correct by post-operative splinting, and it is not one that patients themselves can easily maintain corrected. If the deformity persists, it may cause the head of the femur to slip forwards, and eventually to dislocate—taking the cup with it out of the acetabulum.

The fat female of middle age and beyond, often presents herself with this condition. If operation is agreed, the deformity must be corrected at the time of operation. I am averse from using more machinery than is essential, but if rotation cannot be easily controlled by strapping, I have no hesitation in putting a pin across the upper end of the tibia and applying traction so that the hip is held in its proper position. If post-operative external rotation is allowed, patient and surgeon will qualify for a disappointing time.

The complication actually due to the operation which gives most trouble is the formation of new bone in the operation field, though I think there are some predisposing causes to this condition. If the surgeon is careful to wipe out and wash away as many crumbs of bone as possible at the end of the operation, he will have the minimal formation of new bone. Patients who have a massive osteoarthritis with extensive osteophytes are very liable to produce post-operative masses of bone. The surgeon therefore should not anticipate the best range of movement in these cases and the patient should be forewarned. Extra-special manual care is required when operating on this type of case.

Sometimes bone forms without any obvious cause, and it may be that some patients develop an ossifying myositis in the same way that others develop a myositis ossificans after a dislocation of the elbow. I think that even the most dexterous and careful surgeon will from time to time have trouble due to this cause.

Post-operative care is important as a preventive of new bone formation, and in the cases when the formation of new bone may be suspected, post-operative movements should be delayed and done more slowly and carefully than usual.

Dr. T. G. Reah (Harrogate): I shall consider briefly three groups of patients with osteoarthritis of the hip. There are first those with lesser degrees of pain and stiffness who, on examination, show only a moderate restriction of the movements of the affected joint and whose radiograms reveal the early changes of arthritis. Such patients not infrequently present themselves before the age of 50 but they also occur in the older age-groups. We have already heard from Dr. Tegner of the possible need of a complete readjustment of the patient's life but this may be difficult to attain; as with patients suffering from angina of effort or early heart failure, so must these patients learn to live within their physical capacity. Many of our hospital patients are drawn from a rural area and fitted only for agricultural work so that, in spite of the co-operation of the Disablement Re-settlement Officer of the Ministry of Labour, it is almost impossible to find other suitable work for them. The housing problem again makes it difficult to re-settle these patients. This is our local problem but I have no doubt that each district, whether it draws its patients from an industrial or a rural area, has similar difficulties when an attempt is made to find employment within the capacity of the patient. In general, therefore, these patients in the younger age-group have to restrict their activities but they certainly have not to be allowed to become incapacitated and some of them, particularly the obese women, must be encouraged to exert themselves.

It is in osteoarthritis of the hip at this stage that hydrotherapy is not only one of the most useful therapeutic procedures but probably achieves its own greatest usefulness. The principles of hydrotherapy are quite simple—the buoyancy of the water considerably reduces the force of gravity, muscle spasm is diminished and pain relieved. Other factors involving the peripheral vessels and nerves may be of importance but I think that the three

factors I have mentioned are quite the most important. There are a few contra-indications to hydrotherapy: the presence of fever, physical debility, chronic lung disease and some cardiovascular lesions, and they are usually self-evident.

The simplest form of hydrotherapy is the ordinary bath at a temperature of 100°–102° F. (37·8°–38·9° C.) for twenty minutes and while the patient is in the bath an underwater douche can be given either continuously over the affected joint at a temperature of 104° F. (40° C.) or, a method I prefer, for the last five minutes at 108°–110° F. (42·2°–43·3° C.).

After a period of rest, local massage and movements of the affected joint may be given, again to be followed by a period of rest.

In the Hubbard Tank, or one of its modifications, and in the Deep Pool Bath underwater therapeutic exercises may be performed and I need not elaborate the technical details of their application except to emphasize their usefulness when they are available. Massage douches, such as the Aix, Vichy and Scotch Douche, probably only have a limited application in the treatment of osteoarthritis of the hip unless it is associated with some other disability.

Peloids, a term used to describe peats and muds used for therapeutic purposes, may be used as packs or baths. Packs have little use in osteoarthritis of the hip but peat baths are valuable. The peat is ground up, and then heated to the required temperature by steam or admixture with hot water. Peat has an advantage over water in that it has a low specific heat and therefore a higher temperature can be better tolerated while, because of its poor conductivity, the heat is retained and the bath cools only very slowly. Muscular relaxation and relief of pain are evident but limb movements obviously are impossible. Again, massage after a brief period of rest along with movements of the affected hip-joint through its fullest possible range without the production of pain should be given. After the completion of the bath and massage, be it a water bath with underwater douching or a peat bath, a more prolonged period of rest is desirable. In general, hydrotherapy of the type I have been describing is probably best given in short courses rather than for prolonged periods. The treatments are time-consuming and may be tiring and are therefore not suitable for those who are otherwise engaged in daily work. A period of two or three weeks once or twice each year when daily treatments may be given is probably the optimum course. In the intervening months the usual physiotherapeutic measures already described may be given.

In the second group of patients, those between the ages of 50 and 65, treatment may be as I have just described but, with increasing years, the patient's pain and disability may also be increasing and it is within this group that we find the majority of those on whom surgical procedures have to be considered. In addition to the essentially surgical aspects of the selection of patients, these are the medical problems involved and these are rather greater than a mere assessment of the patient as an anæsthetic risk. Because of the comparative severity of the operation and the prolonged convalescence, I believe that the patients should otherwise have a reasonable expectation of life. The cardiovascular system should be healthy but a moderate degree of hypertension need not contra-indicate operation while the renal function should be satisfactory. A mild degree of chronic bronchitis and emphysema is not a bar to operation but it is advisable for such patients to have a pre-operative course of breathing exercises under the supervision of a physiotherapist, and they should also stop smoking. In all cases, a radiological examination of the chest should be made before operation. Well controlled diabetes mellitus need not contra-indicate operation, but I think that it would be hazardous to risk operation in one whose diabetes is not readily controlled.

If, at this stage, shortening of the affected limb is occurring, elevation of the shoe has to be considered but if there is more than 1 in. (2·5 cm.) shortening, the raise should not be equal to the amount of shortening as some unbalance may be caused because of the compensatory scoliosis which has gradually been developing.

The third group, those patients over the age of 65, present a problem to which the answer is difficult. Often mentally alert and at first anxious to lead more active lives, with the passing of time they tend to restrict their activities and it becomes difficult to persuade them to lead a life in which rest and movement are suitably combined but it is important to encourage them to move about to the limit of their capacity. When resting, the recumbent is better than the sitting position and a firm mattress better to sleep upon than a soft one. Hydrotherapy may still be of use in the older patients but only with care, particularly in those over the age of 70 and, in any case, both the duration of the treatments and the temperatures at which they are given must be modified as compared to those used in younger patients. While the diagnosis of osteoarthritis of the hip in the elderly is now more than a matter of faith, we must still admit with Robert Hutchison that the prognosis is a question of hope and the treatment only too often an affair of charity.

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Section of Surgery

President—Sir STANFORD CADE, K.B.E., C.B., F.R.C.S.

[*November* 1, 1950]

Soft Tissue Tumours: Their Natural History and Treatment

PRESIDENT'S ADDRESS

By Sir STANFORD CADE, K.B.E., C.B., F.R.C.S.

ABSTRACT.—A series of 153 patients, the largest yet recorded from a single source, suffering from soft tissue sarcoma is discussed. References to the literature show the rarity of such tumours, the vagueness of the nomenclature and the disappointing results of treatment. Of the 153 patients only 7 have no histological confirmation of the diagnosis. In 146, sections and histological reports are available. 148 patients have been followed up either to death or to date.

The author defines soft tissue sarcoma as a tumour of mesenchymal origin arising in association with the connective tissue of the fasciæ, aponeurosis, tendon sheaths, intermuscular septa, voluntary muscles and synovial membrane. Histologically they are classified as

	Cases
Spindle-cell sarcoma	42
Fibrosarcoma	48
Myxosarcoma	11
Synovioma	11
Liposarcoma	7
Neurogenic sarcoma	9
Rhabdomyosarcoma	7
Various	11
No histology	7
Total	153

The term spindle-cell sarcoma should not be used to describe a tumour entity as by "using such a term the reporter confesses his inability to recognize the nature of the tumour". The author also condemns the use of the term "neurogenic sarcoma" to describe a soft tissue sarcoma unless it is derived from peripheral nerves. The 9 cases of neurogenic sarcoma in the author's list had no definite diagnostic features in the sections except for the arrangement of fibres in "whorls". Again the term myxosarcoma is misleading as such a tumour, chiefly composed of fibroblasts with areas of mucoid degeneration, is not a definite clinical entity.

The greatest incidence is between 20 and 30 years of age, but they may occur in infants a few weeks old, in whom fortunately the prognosis is not always hopeless.

The sex incidence shows a preponderance in men for tumours of trunk and limbs. In other sites the sex incidence is equal. The site incidence shows that the majority occur in the limbs, the lower limb being the commonest site of all. Prognosis is most favourable for tumours in limbs and trunk.

Fibrosarcoma (the commonest type) is derived from fibroblasts. It is composed of spindle cells with an elongated nucleus. Metastases are multiple and widespread. Synovial sarcoma has a distinct histology. It occurs in connexion with bursæ, tendon sheaths or joints. Its prognosis is worse than that of fibrosarcoma.

Liposarcoma is rare. Main features are foamy embryonal fat cells, rapidity of growth and great size.

Rhabdomyosarcoma may be of two varieties—cells with longitudinal and cross striation, and broad ribbon cells.

Angiosarcoma is markedly vascular.

Three main methods of treatment were used : (1) Wide excision in association with radiotherapy, both pre- and post-operative; (2) Amputation, alone or with radiation; (3) Radiation only. Local excision by enucleation proved to be a failure owing to recurrence. Knowledge of the histological type is important for prognosis. Amputation is not a "cure". Neither should radiation *alone* be advised where wide excision is possible.

In this series survival up to 26 years has been obtained and half the patients have been salvaged.

The author suggests that radiation in moderate doses over long periods breaks the chromosomes, thus causing gene mutations and in time the cells become non-reproductive. Sublethal radiation may also produce chemical intracellular changes resulting in sterility of the malignant cells.

The author's results showed a longer survival after conservative excision and radiation than after amputation.

RÉSUMÉ.—Discussion sur une série de 153 cas de sarcome des parties molles, la plus longue provenant d'une seule source rapportée jusqu'ici. La rareté des tumeurs de ce genre, le manque de précision de la nomenclature et les résultats décevants du traitement sont démontrés par des allusions à la littérature. Parmi ces 153 cas il n'y en a que 7 où le diagnostic n'a pas été prouvé par l'examen histologique. Il existe des sections ou des rapports histologiques pour 146 cas. 148 malades ont été suivis jusqu'à présent ou jusqu'à leur décès.

L'auteur définit le sarcome des parties molles comme une tumeur d'origine mésenchymale, se produisant en rapport avec le tissu conjonctif des aponévroses, des gaînes tendineuses, des cloisons intermusculaires et des membranes synoviales. Leur classification histologique est la suivante:

	Cas
Sarcome fuso-cellulaire	42
Fibro-sarcome	48
Myxosarcome	11
Synoviome	11
Liposarcome	7
Sarcome neurogène	9
Sarcome rhabdomyoblastique	7
Divers	11
Sans examen histologique	7

Le terme "sarcome fuso-cellulaire" ne devrait pas être employé pour décrire une entité tumorale, car "par l'emploi d'un tel terme l'auteur s'avoue incapable de reconnaître la nature de la tumeur". L'auteur condamne aussi l'emploi du terme "sarcome neurogène" comme description d'une tumeur des parties molles à moins qu'elle provienne d'un nerf périphérique. Dans les 9 cas de sarcome neurogène dans la liste de l'auteur le seul caractère diagnostic défini est l'arrangement des fibres en "spirales". De plus, le terme myxosarcome est trompeur, car une tumeur de cette espèce, composée principalement de fibroblastes avec des plages de dégénérescence mucoïde, n'est pas une entité clinique bien déterminée.

L'incidence maximum de ces tumeurs est entre les âges de 20 et 30 ans, mais elles peuvent survenir chez des enfants de quelques semaines, chez lesquels le pronostic n'est heureusement pas toujours fatal.

L'incidence d'après le sexe montre que les tumeurs du tronc et des membres sont plus fréquentes chez les hommes. Pour les autres situations la fréquence est la même chez les deux sexes. Le pronostic est le plus favorable dans les tumeurs des membres et du tronc.

Le fibro-sarcome (le type le plus fréquent) provient des fibroblastes. Il consiste en cellules fusiformes à noyau allongé. Les métastases sont multiples et largement répandues. Le

sarcome synovial a une histologie spéciale. Il survient en relation avec les bourses synoviales, les gaînes des tendons ou les articulations. Le pronostic est moins favorable que celui des fibro-sarcomes.

Le liposarcome est rare. Ses principaux caractères sont des cellules graisseuses embryonnaires écumeuses, une croissance rapide et un grand volume.

Le sarcome rhabdomyoblastique peut prendre deux formes, l'une à cellules striées en longueur et en largeur, et l'autre à cellules larges en ruban.

L'angiosarcome présente une vascularisation prononcée.

Pour le traitement, trois méthodes principales ont été employées: (1) l'excision large avec radiothérapie pré- et post-opératoire, (2) l'amputation, seule ou avec radiothérapie, (3) la radiothérapie seule. L'excision locale par énucléation s'est montrée inefficace à cause de récidives. Il est important de connaître le type de la tumeur pour déterminer le pronostic. L'amputation n'assure pas la guérison. La radiothérapie seule n'est pas non plus à recommander si l'excision large est possible.

Dans cette série de cas des survies de jusqu'à 26 ans ont été obtenues, et la moitié des malades ont été sauvés.

L'auteur suggère que l'irradiation prolongée peu intense et à doses modérées détruit les chromosomes, produisant par ce fait une mutation des gènes, et qu'avec le temps les cellules perdent le pouvoir de se reproduire. L'irradiation sous-léthale peut aussi produire des changements chimiques intra-cellulaires aboutissant à la stérilité des cellules malignes.

Les résultats obtenus par l'auteur montrent une plus longue survie après l'excision large avec radiothérapie qu'après l'amputation.

RESUMEN.—Se discute una serie de 153 pacientes, la mayor hasta ahora registrada procedente de una única fuente, afectos de sarcoma de tejidos blandos. Las referencias en la literatura muestran la rareza de estos tumores, la falta de claridad en la nomenclatura y los desilusionantes resultados del tratamiento. De los 153 pacientes, solamente en siete casos faltaba una confirmación histológica del diagnóstico. En 146 casos se dispone de preparaciones e informes histológicos. 148 pacientes han sido observados hasta su muerte o hasta la fecha.

El autor define el sarcoma de los tejidos blandos como un tumor, de origen mesenquimatoso, que aparece en asociación con el tejido conjuntivo de fascias, aponeurosis, vainas tendinosas, septos intermusculares, musculatura esquelética y membranas sinoviales. Histologicamente se clasifican como:

Sarcoma fusocelular	42
Fibrosarcoma	48
Mixosarcoma	11
Sinovioma	11
Liposarcoma	7
Sarcoma neurogénico	9
Rabdomiosarcoma	7
Varios	11
Sin diagnóstico histológico	7

El término "sarcoma fusocelular" no debe usarse para describir una entidad tumoral "como si usando tal terminología confesase el observador su incapacidad para averiguar la naturaleza del tumor". El autor condena, asimismo, el uso del término "sarcoma neurogénico" para describir un sarcoma de tejido blando, a no ser que éste haya derivado de los nervios periféricos. Los nueve casos de sarcoma neurogénico en los protocolos del autor, tienen como única característica diagnóstica definida la disposición de sus fibras en "torbellinos". El término "mixosarcoma" es igualmente equívoco, puesto que tal tumor, compuesto principalmente de fibroblastos con areas de degeneración mucoide, no es una entidad clínica definida.

La mayor incidencia de estos tumores ocurre entre los 20 y 30 años de edad, aunque también pueden aparecer en niños de pocas semanas, en los que el pronóstico, afortunadamente, no es siempre desesperado.

En el varón estos tumores se localizan, preponderantemente, en el tronco y las extremidades. La incidencia de los que se localizan en otras regiones es igual en ambos sexos. En general,

la mayoría de ellos se desarrollan en las extremidades, siendo las piernas su localización más frecuente. El pronóstico es más favorable en los tumores de las extremidades y tronco.

El fibrosarcoma (el tipo más común) deriva de los fibroblastos. Está formado por células fusiformes, con nucleo alargado. Las metástasis son múltiples y diseminadas. El sarcoma sinovial tiene una histología típica; aparece en las bolsas sinoviales y vainas tendinosas o articulares. Su pronóstico es peor que el del fibrosarcoma.

El liposarcoma es raro; sus principales características son: células adiposas embrionarias, de aspecto espumoso, rapidez de crecimiento y gran tamaño.

El rabdomiosarcoma puede ser de dos tipos—células con estriación longitudinal y cruzada, el uno, y anchas células en forma de cinta, en el otro-.

El angiosarcoma es marcadamente vascular.

Los tres métodos de tratamiento principalmente usados son: (1) Amplia ablación asociada a radioterapia, pre y postoperatoria; (2) Amputación, unida o no a radioterapia; (3) Radioterapia unicamente. La extirpación local, por enucleación, no ha dado resultado debido a las recidivas. El conocimiento del tipo histológico es de importancia para el pronóstico. La amputación no es una cura, como tampoco lo es la radioterapia, recomendable solamente cuando una amplia extirpación es posible.

En la serie estudiada se han conseguido supervivencias hasta de 26 años, habiendo sido salvados la mitad de los pacientes.

El autor sugiere que la radioterapia en dosis moderadas durante largos periodos rompe los cromosomas, causando de esta manera la mutación de los genes, y al cabo del tiempo las células pierden su capacidad reproductora. Una irradiación subletal puede producir tambien cambios químicos intracelulares que determinan la esterilidad de las células malignas.

Los resultados del autor muestran una mayor sobrevivencia después de una extirpación conservadora unida a radioterapia que después de la amputación.

It has been my good fortune to have had under my care or the joint care with one or other of my colleagues a series of 153 patients suffering from soft tissue sarcoma. The rarity of such tumours can be judged from the literature. The largest series I have been able to find are those of Gunnar Jönsson (1938), 92 collected cases (from Sweden); Moulonguet and Pollosson (1938), 119 cases (from France); Warren and Sommer (1936), 150 cases; and Nathanson and Welch (1937), 161 collected cases (in the United States). Personal series are very much smaller; even the surgical giant Gordon-Taylor (1940) could muster only 20 personal cases and 9 others seen by him in consultation up to 1938, and he records that at that time there were in all only 43 other cases at the Middlesex Hospital. My series of 153 patients seems therefore the largest personal number and forms an important group for careful study; it covers a period of thirty years. However, what prompted me to choose "Soft Tissue Sarcoma" as the subject of this Presidential Address is the completeness of the records. Of the 153 patients, only 7 have no histological confirmation of the diagnosis; in 146, sections and histological reports by one or more pathologists are available. Further, only 5 patients are untraced, whereas 148 have been followed up either to death or to date.

Because of their rarity, their complexity of structure and their unpredictable clinical behaviour as compared to the more common types of cancer, the personal experience of most surgeons in this type of tumour is very limited and this limitation is reflected in the literature which usually deals with small groups of cases, in the nomenclature which seems untidy and at the mercy of passing fashions and in the methods of treatment which by their disappointing results have given these tumours a sombre reputation and a gloomy prognosis.

It seemed to me that this series offered an opportunity to assess the present state of our knowledge. The review of the material in the light of experience justifies a reorientation of the clinical ideas, a need for a simplification of the nomenclature and a change in the usual practice as regards treatment.

Nomenclature and Classification

By soft tissue sarcoma is meant a tumour of mesenchymal origin arising in association with the connective tissue of the fasciæ aponeurosis, tendon sheaths, intermuscular septa, voluntary muscles and synovial membrane. It is of course known that similar types of tumour do occur in other sites: the skin, the breast, the mesentery, the gut, the omentum, even the brain; but this study is not concerned with these sites. The histological structure of these tumours varies and in my series the following names were used in the pathological reports.

TABLE I.—SOFT TISSUE SARCOMA—HISTOLOGY IN 153 CASES

Spindle-cell sarcoma	42
Fibrosarcoma	48
Myxosarcoma	11
Synovioma	11
Liposarcoma	7
Neurogenic sarcoma	9
Rhabdomyosarcoma	7
Various	11
No histology	7

The heading "various" in Table I included "angioendothelioma", "angiosarcoma", "perithelioma", "hæmangioendothelioma" and compound names of any two or more, such as "lipo-myxosarcoma", &c., and some others as bizarre and obscure as the histological picture itself.

It is of course open to the pathologist to use any one of these names; it should be equally open to the clinician to reject some of them as of little value in practice. The histologist can label the tumour by a descriptive term, such as the shape of the most common cell of the tumour; or base his nomenclature on the genesis of the cell. Descriptive and histogenetic terms are sometimes complementary.

The commonest term used is "spindle-cell sarcoma". I suggest that this term, although accurate descriptively, is valueless from the clinical point of view and should not be used to indicate a tumour entity. There are other tumours composed of spindle cells with marked pleomorphism such as osteogenic sarcoma, where this term is not used as an identification mark; yet others, not derived from mesenchyme, such as tumours of neuro-ectodermal origin, which are composed of spindle cells. Stout (1948), the most experienced tumour histologist in the United States does not hesitate to say that by using the term "spindle-cell sarcoma" the reporter confesses his inability to recognize the nature of the tumour.

Neither am I alone in rejecting the term "neurogenic sarcoma" commonly used for the histological identification of soft tissue sarcoma. I am fully aware that this term represents the concept of no less a pathologist than James Ewing himself; that it was supported and popularized by Quick and Cutler (1927), Stewart and Copeland (1931); that it emanated from the Memorial Hospital; that it was accepted by all and sundry; has found its way into text-books and monographs; has enjoyed a popularity quite undeserved for twenty-five years, although now somewhat on the wane. I reject it nevertheless and I do so in company of Gunnar Jönsson (1938) of the Radiumhemmet who states "the author has not adopted the theory of neurogenic origin", and again with Stout (1948) who says: "Thus since the term (neurogenic sarcoma) is a chimera, it will serve only as a bar to progress as long as it continues to be used." It is also significant that in the Panel Discussion on "Soft Part Tumours" at the National Cancer Conference in Memphis, Tennessee, in 1949, it was recorded that "after a recent review of several hundred tumours previously classified at the Memorial Hospital as neurogenic sarcoma, most of the tumours were removed from this category and the remaining are now designated 'schwannoma' ". It is, of course, obvious that neurogenic sarcomas exist, but there must be some evidence that they are derived from peripheral nerves, and there should be more definite criteria by which they can be recognized. It is, besides, unreasonable to accept the theory that most tumours originating in fasciæ, aponeurosis, tendon sheaths, perimesium, intermuscular septa, should, in fact, not arise from these structures at all, but from the nerves in their vicinity. As a clinician, I am of course not concerned primarily with the actual "label" of a tumour but with the significance of such a label in relation to the prognosis and to the choice of treatment. The 9 cases labelled neurogenic sarcoma in this series, now included in the fibrosarcoma group, were therefore very carefully reviewed. The following points were noted: In all 9 cases the tumour was composed of spindle cells, indistinguishable under high power from the spindle cells in other sarcoma. In all 9 cases there was a distinct arrangement described as "whorled" or "pallisade". This arrangement (Fig. 1B) is shown in several monographs as an illustration of a fibrosarcoma and attention is drawn to the fact that the bundle of cells and fibres bend sharply and at right angles when they meet. The 9 cases were submitted to various pathologists and the same section on several occasions was variously reported as "sarcoma", "neurinoma", "neurogenic sarcoma", "neurofibroma", "fibrosarcoma", or even "myxosarcoma". Except for the whorled arrangement (Fig. 1B) of fibres there seems to be no definite diagnostic feature in the sections. On the clinical side, the tumours were situated in close proximity to muscles, or intermuscular spaces in the following sites: vastus medialis, sartorius, tensor fasciæ femoris, quadriceps, Scarpa's triangle, biceps, triceps, scalene muscles. All the cases received

much the same treatment as other patients labelled "fibrosarcoma". Of the 9 patients, 4 died with metastases, chiefly in the lungs, in periods up to two years; 5 are alive for periods of ten, nine, four, four, and two years, and 2 of these are alive with disease. Clinically there is no difference between these patients and the majority of the fibrosarcoma group. They are neither more nor less malignant; survival of ten and nine years has been achieved in some and in others death from metastasis noted. The descriptive term "spindle-cell sarcoma" even when adumbrated by the prefix "large" or "small" and joined to the term "neurogenic" does nothing to clarify our knowledge of the tumour.

To my list of negations I will add one more: "myxosarcoma". Whereas a "myxoma" is a true neoplasm, "composed of stellate cells set in a loose mucoid stroma through which course very delicate reticulum fibres" (Purdy Stout, 1948), a tumour which does not metastasize and occurs commonly in the heart (110 recorded cases), the skin and elsewhere; the so-called "myxosarcoma" is, in fact, a tumour chiefly composed of fibroblasts, showing areas of mucoid degeneration (Fig. 1c). It is not a specific clinical entity. As Willis (1948) points out: "There is no such cell as a 'myxoblast' distinct from the 'fibroblast'." But even with the rejection of these various terms from the nomenclature of soft tissue tumours, there remains quite a list of different varieties.

TABLE II.—HISTOLOGY (REVISED)—146 CONFIRMATORY HISTOLOGICAL REPORTS ON 153 PATIENTS

Fibrosarcoma	112
Synovial sarcoma	11
Liposarcoma	6
Rhabdomyosarcoma	7
Angiosarcoma	10

Before considering in some detail the main features concerning the structure and behaviour of each subgroup it is convenient to summarize briefly some factors applicable to the whole group.

AGE AND SEX INCIDENCE

No age is immune. These tumours occur from birth to old age; the greatest incidence is between 20 and 30 years, but each decade between 10 and 50 years is also represented.

TABLE III.—SOFT TISSUE SARCOMA—AGE INCIDENCE IN 153 CASES

Age	Number of cases
– 5	8
6–10	5
11–20	21
21–30	33
31–40	26
41–50	22
51–60	20
61–70	12
over 71	6

Attention must be drawn to the occurrence of these tumours in infants a few weeks or months old and it is important to point out that the prognosis in these very young patients is not always as hopeless as it is believed to be and that they are amenable to treatment and some survive to adult life without recurrence.

The sex incidence shows a preponderance in men; of the total 153 patients, 86 were male and 67 female. It is interesting to note that this preponderance in men applies only to the tumours in the trunk and limbs, whereas in "odd" sites, head and neck, retroperitoneal and in multiple tumours, the sex incidence is equal.

SITE INCIDENCE OF SOFT TISSUE TUMOURS

The majority of soft tissue tumours occur in the limbs. Table IV shows the site incidence. Over half of the total were found in the lower limb, a quarter in the upper limb; 11% in the trunk, head and neck and a similar number in miscellaneous sites, such as the palate, orbit, &c.

FIG. 1A.—× 70.

FIG. 1B.—× 70.

FIG. 1C.—×140.

FIG. 1.—Fibrosarcoma. All three sections are composed of spindle cells. (A) Is described in most books as spindle-cell sarcoma. (B) Shows characteristic "whorling" which suggests a neurogenic origin but identical histological appearance in French literature is shown as "typical fibrosarcoma". (C) Spindle-cell tumour shows myxomatous degeneration, a few giant cells and some pleomorphism. This is often described as myxosarcoma.
In fact all three sections represent variations of the same tumour, viz. a fibrosarcoma.

FIG. 2A.—Tumour of the back. The scar of a previous operation is seen. This is the usual occurrence following enucleation.

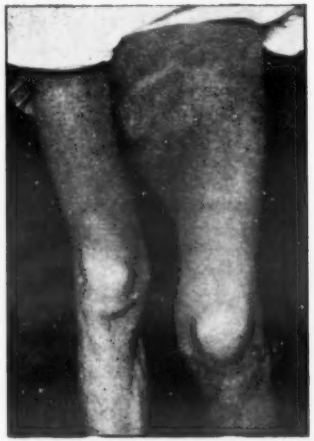

FIG. 2B.—Fibrosarcoma, adductor group of muscles, bone not involved.

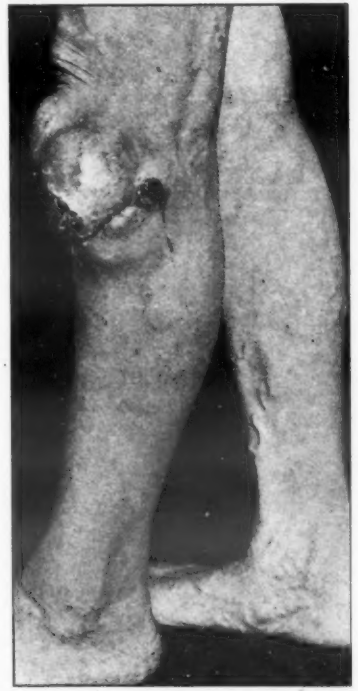

FIG. 2C.—Cystic and myxomatous degeneration of fibrosarcoma outer side of knee.

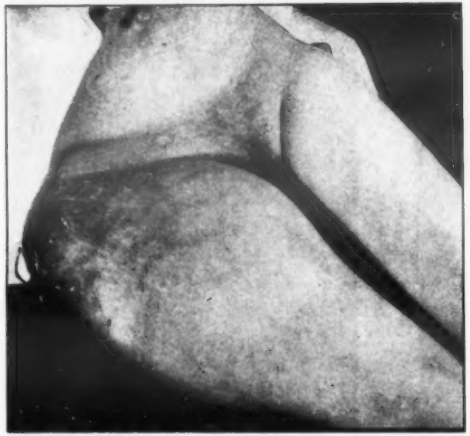

FIG. 2D.—Liposarcoma. The very large size of tumour is illustrated, also the marked venous congestion.

FIG. 2E.—Small tumour dorsum of foot. This insignificant looking fibrosarcoma gave rise to both lymph-node metastases in the groin and blood-borne dissemination, chiefly in the lungs.

FIG. 2.—Clinical appearances of soft tissue tumours.

TABLE IV.—SOFT TISSUE SARCOMA—SITE INCIDENCE IN 153 CASES

Site	No.	%
Lower extremity	80	52·3
Upper extremity	38	24·8
Trunk	11	7·2
Head and neck	6	3·9
Miscellaneous (orbit, palate, retroperitoneal, multiple, &c.)	18	11·8

Various points of interest emerge from an analysis of the site incidence. Thus the survival rates are far fewer in the "odd" sites and the length of survival far shorter than in the limbs, trunk and head and neck. Of 135 cases with such tumours 63 died of the disease; but of these one-third lived more than five years (five to twenty-two years) and under half of the total of deaths occurred in less than two years. The outlook in the "odd" sites is far worse; thus 14 of 18 cases died; half in the first year and the other half in the second year. Thus 80% of soft tissue sarcoma in odd sites caused death within two years from the onset of the disease.

A more detailed study of the site incidence is of practical interest as it affects the actual operative treatment. It is convenient, whenever possible, to localize the tumour to the muscle or muscle group where it is situated; it should be understood that it is not meant that the tumour is actually localized to the muscle in question and lies within it, although this does occur in a proportion of cases; in most it is the connective tissue around the muscle or between muscle groups which at first harbours the tumour. Eventually, it penetrates, invades or spreads along muscle planes. Thus the anatomical names of muscles should be taken as referring to a region. With this understanding the site incidence can be broken down as follows:

Lower limb.—This is the commonest site of all (Fig. 2, B, C, D, E); 80 patients or 52·3% of the total developed a tumour in the lower limb. Of these the quadriceps extensor group accounted for 16 cases, of which 6 were actually in the vastus medialis. Next in frequency were the glutei muscles and the gastrocnemius group, 11 cases in each. The details of the remaining sites are shown in Table V.

TABLE V.—SOFT TISSUE SARCOMA—SITE INCIDENCE IN 153 CASES

Lower Limb

Quadriceps	10
Vastus medialis	6
Gastrocnemius	11
Glutei	11
Sartorius Tensor fascia femoris	8
Scarpa's triangle	7
Adductors thigh	7
Hamstrings	3
Popliteal space	5
Leg (outer side)	3
Knee region	4
Ankle region	1
Big toe	2
Dorsum foot	2
Total	80 = 52·3%

In the early stages of the disease, it is possible to excise a section of the musculature including the tumour and a good, adequate surrounding margin without damage to the main blood supply of the limb and often with a good functional result. This is specially applicable to tumours of the buttock, where after preliminary ligation of the internal iliac artery, the three glutei can be excised very nearly *in toto*; the gastrocnemius, vastus medialis, the sartorius and tensor fascia femoris can also be dealt with that way with surprisingly little subsequent functional disability.

In the upper limb the incidence of tumours is 25% of the total, that is less than half of the incidence in the lower limb. The distribution of the tumour is more limited and is shown in Table VI.

dissemination, chiefly in the lungs.

FIG. 2.—Clinical appearances of soft tissue tumours.

TABLE VI.—SOFT TISSUE SARCOMA—SITE INCIDENCE IN 153 CASES

Upper Limb

Pectoral muscles and chest wall	6
Deltoid—pectoral groove	6
Triceps, biceps, brachialis	6
Extensors forearm (elbow)	7
Extensor and flexor tendon hand and fingers	7
Scapular muscles	5
Flexors forearm	1
Total	38 = 24·8%

The main sites account for about an equal number of cases: pectoral group, scapular muscles, deltoid, the extensors or flexors of the arm or forearm. Here too, provided opportunities are not missed and a planned treatment undertaken the first time, an entire group of muscles and, in the case of the scapular group, the scapula itself can be removed and so a wide excision achieved.

The remainder site incidence accounts for a small number in the trunk and in the muscular and aponeurotic tissue of the head and neck.

TABLE VII

Trunk

Abdominal wall	7
Back (erector spinæ)	4
Total	11 = 7·2%

Head and Neck

Sternomastoid, scalene	4
Temporal muscle	1
Masseter	1
Total	6 = 3·9%

To complete the site incidence a small group of 18 cases, 11·8% of the total, occurred in various sites as shown in Table VIII.

TABLE VIII

Miscellaneous

Face and scalp	5
Orbit	3
Palate	3
Retroperitoneal	2
Multiple subcutaneous	2
In von Recklinghausen's disease	3
Total	18 = 11·8%

MAIN FEATURES OF THE VARIOUS TYPES OF SOFT TISSUE SARCOMA

The five types of tumours listed in Table II have different histological and clinical features.

(1) *Fibrosarcoma* (Fig. 1).—This is the commonest type of tumour. It is derived from fibroblasts and is composed of spindle cells with an elongated nucleus. The function of the fibroblast is to form connective tissue, the collagen fibres. The tumours vary in degree of differentiation and anaplasia, mitotic incidence, arrangement of fibres, size of cells, amount of intercellular stroma (Fig. 1, A, B, C). Thus there is a considerable variation in the sections, some resembling adult fibrous tissue, others embryonic cells and some showing considerable pleomorphism, with increased vascular supply and occasional giant cells.

It is suggested that these variations do not justify classifications into various entities under different names, but should be grouped like epithelial tumours into grades of malignancy from the least to the most differentiated. The collagen material can undergo degeneration and give the appearance of structureless areas, the so-called myxomatous degeneration.

The tumours are all invasive, and invasion of fat, muscle and bone is seen. The gross appearance of these tumours is of interest. In the early stages they are rounded, encapsulated, smooth, firm, pink or yellow on section. Their invasive characters are not apparent to the naked eye, except when small satellite nodules are seen. At a later stage, when the tumours are considerable in size, they become elongated as if moulded by the surrounding muscular masses or multilobulated. But even then they seem for a time to respect the adjoining tissues especially blood vessels and nerves. The capsule is still found in the larger tumour, although thin and incomplete; it is no barrier to the spread of the tumour and affords no protection against it. It is misplaced faith in the capsule which permits easy enucleation of the tumour, which is responsible for so much inadequate surgery; inadequate in the sense that it seldom if ever leads to an eradication of the tumour and is invariably followed by local recurrence. The skin over the tumour remains normal for a long time, showing only some venous engorgement (Fig. 2D). Unlike bone sarcoma, local vascularity is not increased; the tumour feeds on one or two isolated vessels at the periphery and from attenuated, insignificant capsular vessels.

In the late stages the tumour breaks down and cystic areas appear, containing blood or serum or myxomatous or collagenous material (Fig. 2C). The tumour is painless, it grows slowly and a history of two or three years is common; although in some cases the growth is more rapid. It is also noted that periods of obvious increase in size are often followed by periods of quiescence. In a proportion of cases a definite history of *injury* at the site of the tumour is obtained. The occurrence of fibrosarcoma as a sequela to old war wounds is well known. Post-radiation scarring too, leads to this type of tumour, although far less commonly than to post-radiation epithelial cancer. This relation between trauma, scarring and fibrosarcoma is now usually accepted; the time interval between the injury and the formation of the tumour varies from a few months to many years. The longest interval recorded is the following case reported by Purdy Stout (1948).

This patient injured his back as a child; at the age of 9 he developed a lump in the scar; at the age of 35, because of rapid recent increase in size, it was excised in London by Lord Lister. The tumour recurred, again grew slowly for years, then more rapidly and at the age of 65 it was again excised, this time at the Presbyterian Hospital, New York. There was no recurrence after that for a further twenty-five years when he was seen by Whipple. The patient was then 91 years of age and a period of eighty-two years had elapsed since the onset of fibrosarcoma.

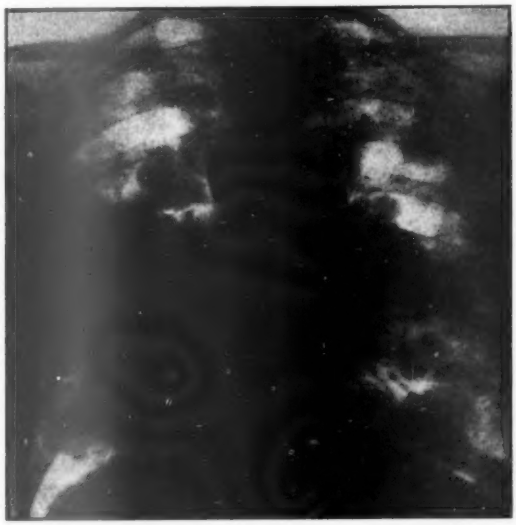

FIG. 3.—Pulmonary metastases from a fibrosarcoma of soft tissue. The variation in size of the metastases indicates that there were repeated embolic deposits throughout a period of several months.

Local recurrence after enucleation is so common as to be the rule (Fig. 2A). In my series several patients submitted to operation six or more times in periods varying from two to fifteen years.

Metastases: Metastases occur chiefly in the lungs but also in the skeleton, lymph glands, liver and in some patients as a terminal phenomenon they are multiple and widespread. There may be a time lag of several years, the longest in my series was eight years, before pulmonary metastasis developed in the absence of any local recurrence. The pulmonary metastases are usually multiple, circumscribed, round shadows, small at first but rapidly becoming the well-known cannon-ball type (Fig. 3). Although both primary tumour and metastases are radioresistant, this is no contra-indication to radiotherapy.

Of the 112 histologically verified fibrosarcomata, 101 occurred in the limbs and trunk; of these 53 are alive and 48 dead; of the 11 cases in odd sites, 8 are dead and only 3 alive.

(2) *Synovial sarcoma.*—The name "Synovioma" was first suggested by Lawrence W. Smith in 1927, but several reports on malignant tumours arising from synovial structures are found in the literature prior to that date (Marsh, 1898; and Lockwood, 1902). Other names "synovialoma", "malignant synovioma", "synovial fibrosarcoma" are used for this tumour. Synovial sarcoma seems the most suitable term and preferable to "synovioma", as the latter may be confused with benign lesions of similar structure.

The distinction between these malignant tumours and others pursuing a benign course was recognized early in this century. These benign lesions, some of them probably inflammatory swellings were described as xanthomata or benign synovioma. Haagensen and Stout (1944) point out that these tumours but seldom arise actually from joint spaces. It is of course well known that they may arise from bursæ and tendon-sheaths. Most authors distinguish two varieties differing in their histological structure. The one showing the characteristics of the tumour, namely tissue resembling, mimicking or caricaturing synovial tissue—slits and spaces lined by cuboidal or even columnar-shaped cells; the other consisting of solid masses of elongated plump spindle cells with considerable vascular spaces (Fig. 4A).

There is a great variation in the amount of fibrosarcomatous elements. Haagensen and Stout's conception of the tumour—that it is "always composed of two sharply contrasted tissue forms, one reproducing caricatures of synovial structures, the other resembling fibrosarcoma and the two are inextricably intermingled" (1944)—is preferable to the subdivision into two different types under the names of "synovialoma" and "synovial fibrosarcoma", both malignant as suggested by Gunnar Jönsson (1938). There is in fact only one type and variations are only in the degree of differentiation and degeneration. If the diagnosis is to be made with confidence many sections should be examined. The histology is so distinct as to suggest that this is a definite tumour entity. This is supported by the clinical features and by the behaviour of the tumour.

The tumours occur most often in connexion with bursæ, tendon sheaths or joints. The history in most cases is of one or two years, but hardly ever longer; in a minority it is of a few months only. The tumour causes slight pain or discomfort but seldom severe pain. If not removed it may grow to a large size—soften and develop cystic spaces filled with blood or serum or jelly-like material. In the 11 patients in my series the sites were : subacromial bursa (delto-pectoral area) 3; elbow-joint 2; hand 2; knee 1 ; tendo achillis 1 ; calf of leg 1; gluteal region 1. Of these 11 patients 4 are dead; 2 alive with disease and 5 free from disease, 1 for five years, 1 for four years, and 3 under three years. The cause of death was metastases in muscles and viscera, including lungs. Of the 104 cases collected by Haagenson and Stout only 3 are known to be free from disease more than five years. Of 32 cases at the Army Institute of Pathology, Washington, 16 were known to have died at the time of reporting but the follow up was at that time incomplete.

Synovial sarcoma is of worse prognosis than fibrosarcoma; they are rare tumours; they show distinct histological features; they cause discomfort but generally slight pain only; they destroy adjoining bone like the fibrosarcomata; they often show small areas of calcifications; they kill within two to four years, chiefly by metastasis; they are radioresistant.

(3) *Liposarcoma.*—This rare tumour is represented six times in this series, an incidence of 4%. In a period of thirty-seven years there were only 41 cases at the Columbia University Laboratory of surgical pathology (A. P. Stout, 1944). Although rare it is a definite entity and presents many interesting points. The characteristic histological feature is the presence of foamy embryonal fat cells (Fig. 4B); this intracellular fat is easily demonstrated in frozen sections and by special staining methods. There are many areas of myxomatous degeneration, and many spindle cells, and so various names are applied to this tumour. "Myxolipoma",

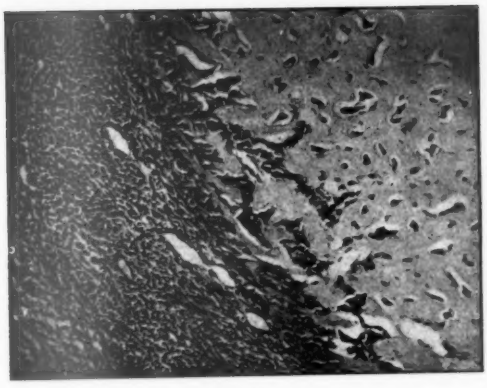

FIG. 4A.

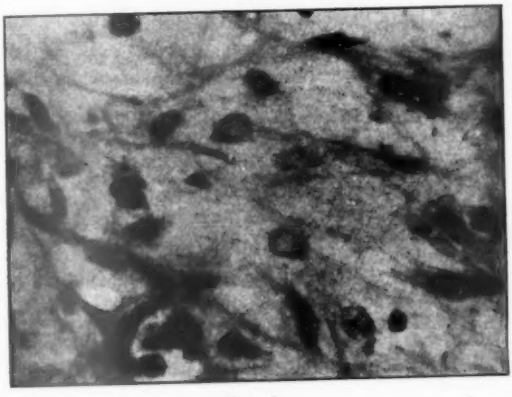

FIG. 4B.

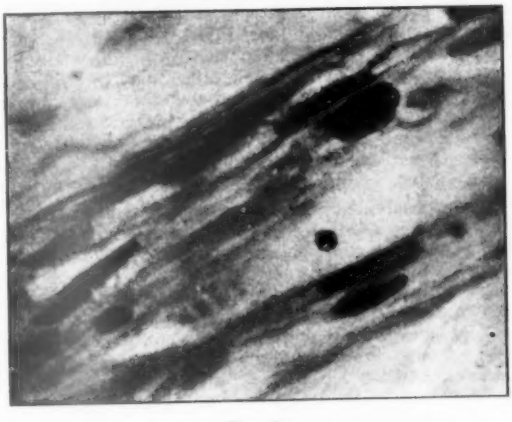

FIG. 4C.

FIG. 4.—The rarer types of soft tissue sarcoma. (A) Synovial sarcoma, showing the characteristic spaces containing cells resembling epithelium; also a solid mass of fusiform cells. × 110. (B) Liposarcoma. This illustrates intracellular fat. × 880. (C) Rhabdomyosarcoma with characteristic cross striation. × 1,024. (Histology by Dr. G. D. Lumb.)

"myxoliposarcoma", "fibromyxolipoma", "embryonic lipoma". Well-differentiated and poorly differentiated myxoid types are described and round-celled tumours of the adenoid type. Some tumours which recur locally and form many satellite masses in the vicinity, invade muscle extensively and even bone, and eventually metastasize, show the histology of a benign lipoma. The macroscopical appearances are also varied; the tumours are bulky and in fact they are the largest soft tissue tumours and may attain an enormous size (Fig. 2D). Their colour is salmon pink, bright yellow, or reddish brown and has been described as the colour of wet chamois leather. They are multilobulated, partially encapsulated, soft with areas of cystic degeneration; the cysts containing fresh or altered blood. They spread inter- or intramuscularly; clinically they are found chiefly in the buttock and thigh; next in frequency are the retroperitoneal or perirenal areas, and occasionally on the upper limb or other sites. They grow rapidly, but show spontaneous periods of growth arrest, an intermittency which is also seen in other varieties of soft tissue sarcomas. Occasionally a liposarcoma occurs as a metaplasia in a pre-existing lipoma, but the majority are malignant *ab initio*.

Metastases occur in the lungs and liver; the age incidence is the 5th and 6th decades, but occasionally the tumour occurs in the younger age-groups; one of my patients was a soldier 19 years of age. Surprisingly, they have been reported as radiosensitive, but I have no personal experience of this. They can grow to an enormous size (Fig. 2D) and A. P. Stout (1944) illustrates a patient reported by Delamater in 1859 where the tumour reached 275 lb. In one of my patients the tumour measured 41 cm. in length and 16 cm. across, and had reached that size in five months.

The main features of this variety are: foamy embryonal fat cells, rapidity of growth, great size; the usual site is the thigh, buttock or retroperitoneal space; the spread along muscle planes and the invasion of muscles; the formation of metastases in soft tissues, including liver and lung. Of the 6 cases, 3 died within eight to twenty months and 3 are alive, the longest only three years.

(4) *Rhabdomyosarcoma.*—Two varieties of cells characterize this tumour; cells with longitudinal and cross striation (Fig. 4C) and broad ribbon-shaped cells with a granular vacuolated cytoplasm, with occasionally part of it striated, the myoblast. Either one or both types of cells can be found in the same tumour. The distinction of two varieties of tumour: the rhabdomyosarcoma and the myoblastoma is hardly justified as careful search of a number of sections nearly always shows both types of cells in the same tumour. Clinically it is the most malignant of all soft tissue tumours and of the 7 cases in my series none survived. 2 occurred in the upper limb and in spite of amputation both died from pulmonary metastases in less than twelve months. They occur in the limbs, but also frequently in the palate, the substance of the cheek, the mouth; they spread rapidly and destroy the surrounding tissues in an astonishing fashion. They appear to be entirely radioresistant. The common age of incidence is in the younger age-group, from 15 to 30 years, but they occur at any age and two of the 7 patients in this series were 50 and 65 years of age respectively.

(5) *Angiosarcoma.*—It is with some diffidence that I decided to include 10 patients under the heading of angiosarcoma. All 10 were reported on histologically as "angiosarcoma", "endothelial sarcoma", "malignant hæmangioendothelioma" or "very vascular round and spindle-cell sarcoma". They have this in common that they were tumours of soft tissue, 8 of them in the muscles and fascial planes of the limbs or back and 2 in the head and neck; 5 patients died of metastasis and 5 are alive for long periods, twenty-one, eighteen, fifteen, fourteen and eight years respectively. It is difficult to decide which of the numerous names applied by different pathologists really represents the nature of the tumour.

It is difficult also to form a definite opinion as to the histogenesis of this group of tumours and the term "angiosarcoma" is used here in a descriptive and not histogenetic sense. All tumours were markedly vascular, some entirely composed of thin-walled cysts filled with blood, lined by a scanty layer of fusiform cells. In 2 patients these cystlike trabeculated tumours had their origin within a muscle and replaced a portion of it. In others the tumour could be described as an extremely vascular spindle-cell sarcoma spreading in the cellular intermuscular planes. Whatever their nature, they seem, at least on gross macroscopic appearance, to fall into a group different from the 4 other types. As to their malignant nature there is, of course, no doubt in the 5 patients who died from metastases: a boy, 19 years of age with a tumour in the calf of the leg, died of pulmonary metastases after amputation; a child 3 years of age with a tumour in her thigh, died within six months and a girl 19 years of age with a tumour in the forearm died with pulmonary metastasis within three years from the onset of the disease; 2 other cases died of widespread disease. Of the 5 patients who have survived for very prolonged periods, one had five local recurrences following local excision before a much wider excision and post-operative radiation controlled the disease.

Results of Treatment

An analysis of the result of treatment is shown in Tables IX, X, XI, XII.

Table IX shows that the prognosis is much better when the tumour is situated in the limbs or trunk than when it arises in the face, mouth, retroperitoneal tissues or when it is multiple in origin.

Table IX.—Soft Tissue Sarcoma

Limbs, trunk, and head and neck ..	Alive	67	patients
	Dead	63	,,
	Untraced ..	5	,,
"Odd" sites	Alive	4	,,
	Dead	14	,,

Table X shows that long periods of survival up to twenty-six years have been obtained; most of the long survivals were actually in cases of fibrosarcoma. These periods of survival are counted from the onset of the disease and not from the last treatment in those cases where recurrence necessitated further treatment.

Table X.—Soft Tissue Sarcoma: Survival

Alive now Free from Disease

20 to 26 years	11	patients
15 to 18 years	12	,,
10 to 14 years	9	,,
5 to 9 years	15	,,
Less than 5 years	20	,,
Total alive	67	patients

Table XI is an analysis of the period of survival in the patients who died of the disease. It shows that 15 patients survived five to nine years and only 8 died within the first year; 2 patients survived twenty-two years. It indicates that even in the fatal cases the progress of the disease is slow in most patients.

Table XI.—Soft Tissue Sarcoma: Deaths

Length of Survival

Died after 22 years	2	patients
,, ,, 10 to 13 years	4	,,
,, ,, 5 to 9 ,, ...	15	,,
,, ,, 2 to 4 ,, ...	21	,,
,, ,, 1 year	13	,,
Died in less than 1 year	8	,,
Total deaths	63	patients

Prognosis

Table XII is an attempt to correlate the histological variety with the prognosis. It supports the previously reported opinion as to the relative malignancy of various groups. The most lethal is the rhabdomyosarcoma which shows no survival.

Table XII.—Soft Tissue Sarcoma—Survival by Histological Type (146 Cases)

	Total	Alive	Dead
Fibrosarcoma	112	57	55
Synovial sarcoma	11	5	6
Liposarcoma	6	2	4
Rhabdomyosarcoma	7	0	7
Angiosarcoma	10	5	5
Total	146	69	77

Methods of Treatment

It was, I thought, of interest to try and correlate the method of treatment with the results obtained. Three main methods were used: (1) Wide excision in association with radiotherapy,

both pre- and post-operative; (2) amputation, alone or with radiation; (3) radiation only. Table XIII shows the results obtained in 128 cases.

TABLE XIII.—METHOD OF TREATMENT AND RESULT IN 128 PATIENTS

	Wide excision with radiation	Amputation with or without radiation	Radiation only
Alive	49	10	6
Dead	31	16	16

It is, of course, obvious that those submitted to amputation were more advanced, or more malignant than those where wide local excision appeared to offer a reasonable chance. Similarly when radiation alone was used, the tumour was either irremovable or there was some other cause why more classical methods of treatment were not adopted. The cases are therefore not strictly comparable and the Table is chiefly of interest in showing the following points: (1) Where wide local excision with radiation was used more patients survived than died; (2) when amputation was carried out, more patients died of their disease than survived; (3) when radiation alone was used 6 patients got rid of their tumour completely, and for very long periods, although 16 did not and died of the disease.

In the light of experience further points were noted and these can be summarized as follows: (1) Whenever local excision by enucleation of the tumour was used, the result was a failure, the tumour recurred and with such repeated local excisions kept on recurring. I am sure that there are many surgeons who have had this experience.

(2) The knowledge of the histological type is of practical importance, as of the five groups, the rarer types consisting of highly specialized cells are the most malignant; and the commonest variety, the fibrosarcoma, offers a more hopeful outlook.

(3) Amputation does by no means result in a "cure" and, as a matter of fact, more patients died of their disease when this method was used than when wide local excision was practised. The indications for amputation are limited; it should be used when a limb is otherwise uneconomical and a burden; when the tumour by its size or site does not lend itself to local excision; when the histological type is such that more conservative measures have proved unsuccessful, for instance rhabdomyosarcoma and liposarcoma.

(4) Neither should radiation *alone* be advised as the method of choice in cases suitable for wide excision. We have not yet reached the stage when radiation can be offered to the patient as equally effective if the tumour can in fact be removed. It is important that the patient should not become a radiotherapeutic guinea-pig, neither should he be a victim of ablational enthusiasm and of surgical heroics.

Radiation as the sole method of treatment is advocated only in a selected group of cases, where surgery is not applicable. 22 patients received radiation only, of these 16 died. The 6 survivals, however, are worth mentioning. In one case, a malignant tumour of the pectoral group of muscles—proved histologically a fibrosarcoma—was treated by radium over a period of three years; she is alive to-day twenty-six years later. Two other patients with tumours in Scarpa's triangle, of similar histology, survived radiotherapy to date, seventeen and fifteen years respectively. One infant 14 weeks old with a tumour in the sternomastoid and invasion of the clavicle with osteolysis of the inner third of the bone, treated by radium survives to date, eighteen years. A case of soft tissue tumour in the region of the head of the fibula treated by radiation only is alive to-day, five years later, and a tumour in the scalene muscles—reported variously as neurogenic sarcoma and fibrosarcoma—irremovable, although explored twice, has regressed following radiotherapy, now in the fifth year after treatment. These cases show clearly that "radioresistance" does not signify that radiotherapy should not be used and that many years of survival can be achieved by radiation alone. Radiation is of considerable value and plays an important part in the treatment and has given results when used in combination with surgery, better than surgery alone, however extensive the surgery. But sarcoma of soft tissue, like bone sarcoma is classed as a "radioresistant" tumour, that is, it requires more radiation to obtain regression as compared to some other tumours. It is in view of this acknowledged "radioresistance" of soft tissue sarcoma, that the meaning of the term "radioresistant" should be reviewed; chiefly it should not be considered as a contra-indication for radiotherapy. This becomes of greater importance with the development of more powerful sources of radiation, more accurate treatment and a better understanding of the mode of action of radiation. It is my experience that fibrosarcoma, like osteogenic sarcoma, if it is to benefit from radiotherapy should be given *less and not more* radiation and that the time factor must be greatly prolonged. The actual technique of treatment is quite different from that used in the treatment of the common epithelial tumours and the highly radiosensitive neoplasms.

I think it is not fortuitous that in this series, survival up to twenty-six years has been obtained and that half the patients have been salvaged. I believe it is due not so much to my enthusiasm as to the biological effects of ionizing energy and to the adjustment of the surgical act, in its extent and the timing of its performance, to the natural history of the tumour and its alteration by pre-operative treatment. It cannot be denied that the results in this series, the largest yet recorded from a single source, are better numerically and in prolongation of the periods with freedom of disease than when surgery alone is used. I have asked myself and I have been asked by many others why delay in surgical treatment, and why pre-operative radiation should affect the issue? There is no certain explanation for this although we have been seeking it for many years. In fact why should the group of cases where this combined and prolonged treatment was carried out, show a smaller incidence of metastases? I venture to offer the following explanation. In epithelial tumours of small volume, for instance cancer of the tongue, a very high total dose of 6,000 r to 10,000 r leads to death of the cancer cells and resorption of the tumour. Such a method is not applicable to large volume tumours, neither is it applicable to the so-called "radioresistant" neoplasms. But penetrating radiation at a lower total dose and especially at a slower dose rate, affects the tissues in other ways or to a different degree. One way of mastering a cancer cell besides killing it outright, is to alter its reproductive rate or power. It is well known that chromosomal breaks result from radiation and of course from other causes such as chemical action, e.g. nitrogen mustard. A chromosomal break if complete and if affecting all cells would result in cancer becoming a self-limiting process. But the breaks in the chromosomes at low dosage levels do heal and this leads to an increase in the number of mutations; this in turn reduces the power of cell division in the daughter cells derived from these and so after a generation or two or more, the end-result is sterility of the cell. Such sterile cells, capable of survival but incapable of reproduction, when disseminated by embolism to the lung or other organs cannot form metastases. Such pulmonary emboli are known to occur during pregnancy when cells of chorionic type are found in the lungs of pregnant women—and yet never form metastases of chorionepithelioma, and disappear spontaneously. If such a process is normal in physiological phenomena, it is possible for it to occur in pathological processes if the cell carried by embolism is actually incapable of reproducing itself. Such an explanation, that gene mutation follows the chromosome break resulting from radiation, is accepted by geneticists. Some geneticists consider that an increased rate of gene mutation, beyond what is needed for the evolution of a species by natural selection, is "wholly bad". Bad for the individual, for the offspring and indeed for the species. If such mutation is wholly bad for normal growth—it is indeed nothing but wholly good in the control of growth of cancer cells. But although an alteration in the nuclear structure of the cells seems a possible explanation, it may not be the correct one. Sublethal radiation may also affect the molecular structure of cells and lead to chemical changes permitting survival of cells but resulting in their sterility. This may explain the beneficial effects of protracted treatment amounting in all to moderate tissue doses. Such treatment is compatible with subsequent surgical excision of the tumour. A wide local excision, including a wide margin of healthy tissue, excision of a complete muscle or muscle group preceded and followed by radiation seems to be the method of choice. An analysis of the patients who died from the disease, shows a substantially longer survival after excision and radiation than after amputation. Thus of the 16 patients submitted to amputation who subsequently died of the disease, only 1 survived nine years, 1 six years, 3 four years, 6 two to three years and 5 less than two years. Whereas of the 31 patients who died of their disease after excision and radiation, 1 each lived thirteen, twelve, ten and nine years, 2 for six years, 8 for five years, 9 for two to three years and 8 for one year or less. I do not know if these figures are statistically significant, but more patients lived for considerable periods, five to thirteen years, with the combination of conservative surgery and radiation, than with amputation.

It seems essential before deciding on a plan of treatment to have an accurate knowledge of the tumour and this can only be achieved by a biopsy, providing ample material for the pathologist.

In conclusion the study of this series of soft tissue sarcoma shows that just over half the patients with tumours in the limbs survived for prolonged periods; that most patients with tumours in odd sites died. That decision as to method of treatment depends on the histology and the site of the tumour. That amputation was indicated in less than a quarter of the total number; that in the common histological type, fibrosarcoma, the disease is of slow evolution and survival periods of many years can be obtained. Perhaps this justifies a more optimistic view than is generally held.

It has also emerged from the study of these tumours and observation of patients over long periods of time, that there is a fundamental difference between the behaviour of sarcoma both of soft tissue and osteogenic and that of epithelial malignant growths. In the case of

cancer of epithelial origin, delay in treatment is detrimental and loses the patient his best chance; not so in sarcoma, here the best end-results are actually seen in the patients in whom for some reason or other there was some delay before surgery was undertaken. If this period of waiting before excising the tumour or amputating the limb is used in radiotherapy, such delay becomes of benefit in a positive sense. It is also of interest to note that several female patients with soft tissue sarcoma in whom arrest of the disease was obtained, subsequently experienced one or more normal pregnancies without recrudescence of tumour activity or recurrence.

Finally I would like to thank those who rendered this study possible, especially Miss P. Wheatley whose care of the notes and follow-up provided a completeness of records which could hardly be surpassed. Dr. G. D. Lumb and Dr. M. Bodian for a review of many histological sections, some over twenty years old, and for their opinion as to the type of tumour. I am indebted to Dr. P. Hansell for the photography of the material. To my clinical colleagues at Westminster Hospital and elsewhere, I owe a debt of gratitude for access to some of the patients in this series and to my friend and colleague Dr. F. M. Allchin for many years of collaboration in the treatment of these patients, especially by radiotherapy. And so to conclude on an optimistic note: Sarcoma of soft tissue in spite of its evil reputation, if treated adequately offers on the whole, a 50% chance of prolonged survival—which is indeed better than in most other groups of cancer.

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Section of Neurology

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The Cerebral Basis of Consciousness. [*Abridged*]

PRESIDENT'S ADDRESS

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What do we mean by consciousness? It is a quality which those states, which we call conscious states, have in common, but there is no reason to suppose that it exists independently of them. There is no such thing as consciousness apart from conscious states, any more than there is redness apart from red objects. My object in this Address is to try in part to answer the question: what is happening in the nervous system when we are experiencing a conscious state?

Local Sign in Sensation

Let us begin by considering what is involved in the simplest possible experience of a bodily sensation, a touch, let us say, on one big toe. It is generally agreed among neurophysiologists that although impulses in the afferent nerves differ somewhat in their rates of conduction there is no substantial difference between them corresponding to differences of sensory quality. It is unlikely, therefore, that it is the character of the electrical impulse in the afferent nerves which tells us that we are being touched, and there is certainly nothing toe-like in the afferent impulses carried by the pathways conducting the sensations of touch from the toe which tells us that it is the toe which is being touched. The anatomist may be able to identify the toe area by tracing pathways of degeneration, the physiologist by detecting the response of the cortex to peripheral stimulation, but this is information derived from the outside. The clinician and pathologist observe that a lesion in a certain area of the sensory cortex causes a loss of feeling in the toe, but this does not explain why it should be so. If we imagine the nervous pathways from the toe to the cortex completely isolated from the rest of the nervous system, it is clear that they could by themselves convey no localizing information, for how could electrical impulses exactly like those going to all the other cortical sensory areas mean that something is happening to the toe? This surely provides a clue to the answer, which is that we can localize touch only by perceiving it in relation to a representation of the body as a whole—whether in the form of unconscious schema or fully conscious image is unimportant for our present purpose—and this body-schema maps out, as it were in a set of co-ordinates, all the possible voluntary actions which we should need to take in order to remove the stimulus either with the other foot or with either hand, or in any other way.

This process of localization of touch is a cortical function, but if I am right in thinking that it relates the touch felt to the body-image as a whole, it must involve pathways far more extensive than the primary sensory areas for touch in the cortex. When, therefore, the cortical area corresponding to one great toe is excited by the arrival there of an afferent impulse resulting from stimulation of the toe itself, such

excitation must cause a widespread irradiation of impulses linking the toe area with the parieto-occipital areas which are concerned with awareness of the body-image, not only in the same cerebral hemisphere but by way of the corpus callosum with the corresponding area on the opposite side of the brain. The same thing must happen if the cortical sensory area is excited by an epileptic discharge or by an attack of migraine. And this, I take it, was what Hughlings Jackson (1931) meant when he said: "I must submit that the units making up that division of the highest centres which I call the anatomical substrata of subject-consciousness represent (properly rerepresent) all parts of the body, mainly sensorily, *in relation to one another*." And again, speaking of a prick on the back, "physically, the nervous impulses starting from a point on the periphery pricked 'travel' to units of the highest centres *universally* representing, and not to units representing one part of the back only. . . . In general the anatomical substrata of subject-consciousness are centres of universal co-ordination, or, as we said, they are unifying or synthesizing centres". Hence, when we speak of a part of the body as being represented for purposes of sensation at a certain point in the postcentral convolution on the opposite side, we do not mean that the consciousness of a part of the body is in some way localized there but that the cortical area in question constitutes a nodal point at which the sensory impulses coming from a particular part of the body are brought into relation with the whole body-image by means of pathways which must ramify widely throughout the posterior halves of both cerebral hemispheres to reach Jackson's division of the highest centres, the "anatomical substrata of subject-consciousness" rerepresenting all parts of the body in relation to one another.

So far reflection takes us. Is there any physiological evidence in favour of such a view? Adrian (1940, 1941) and Woolsey and his collaborators (Woolsey and Fairman, 1946; Woolsey, 1947) by using electrocorticography to map the responses to sensory stimulation have demonstrated the existence of two cortical sensory areas in each hemisphere, which they call somatic areas 1 and 2. Area 1 which appears to correspond to the postcentral cortex in man is strictly contralateral in its representation except for a bilateral representation of the face area. Area 2 represents both sides of the body, but the contralateral twice as much as the ipsilateral. French, Sugar and Chusid (1947) have shown that area 2 has connexions with the pre- and post-central areas of the same and the opposite hemisphere. We do not yet know the function of the somatic area 2 but it is tempting to believe that it is concerned with the relation of primary sensory stimuli to the body-schema.

Imagery and Memory

A good deal has been written recently about the disorders or the body-image itself and the main facts are now generally known. The most bizarre of these is the failure to attend to, or in extreme cases even to recognize as part of the body, the limbs on the left side as a result of a lesion in the right parieto-occipital region. There is one important conclusion which can be drawn from cases of this kind, viz. that the lesion in such cases has destroyed not only the patient's present awareness of his body-image but also neurones which are essential to his ability to remember that he ever possessed a left half of the body. If this is a true interpretation it would seem that the process of remembering the body-image involves an activation of the same neurones as are concerned in its current awareness.

What happens in the brain when we exercise visual imagination, when we create a visual image of some past event or even of something purely imaginary? Electro-encephalography provides a clue in the fact that the exercise of the imagination interferes with the alpha rhythm which is regarded as indicating a state of rest in the visual cortex.

It sometimes happens that as a result of a lesion of the brain a patient loses all visual imagery, which can no longer be evoked voluntarily and ceases to occur spontaneously. This condition has also been called loss of revisualization (Nielsen, 1946).

Nielsen states that the lesion responsible for loss of revisualization involves Brodmann's area 19. Pitts and McCulloch (1947) say that during stimulation of a single spot in area 18 "human patients report perceiving complete and well-defined objects, but without definite size or position, much as in ordinary visual mental imagery" (*see also* Bonin, Garol and McCulloch, 1942). We do not yet know enough about the functions of the parastriate region to be dogmatic, but there is evidence which suggests that visual imagery may depend upon the integrity of that part of the brain. Whether the image is, as it were, displayed upon the visual cortex or utilizes a secondary visual area we do not yet know.

Penfield's (1947) observation that it was possible to evoke in a patient an elaborate visual picture of a remembered scene by electrical stimulation of the temporal lobe takes us a step further towards the anatomy of memory. So we seem led to picture the anatomical basis of memory, so far as it involves images, as innervating widespread areas of the cortex, including in all probability the relevant primary sensory areas. Dreaming must involve in part the same pathways. Clearly it would be quite erroneous to picture either memories or images as "stored" in some area of the brain. We should think rather of a widespread neural network which can be set vibrating in an almost infinite variety of patterns in space and time.

Consciousness and Patterns

One of the most fundamental properties of the brain is that which renders possible the recognition of patterns. The biological importance of this is obvious on a little reflection. Objects of the same kind differ among themselves. Cats, for example, are not all alike. Survival, however, often depends upon the ability of the organism to react to all objects of a class in the same way. Clearly it would be impossible for the nervous system to be so organized that the appropriate reaction should be directly linked with each group of stimuli representing each of the various individuals of a given class. The organization required would be too complex. Such reactions could not be innate nor could they be learned by experience, because each fresh individual member of the group would constitute a new group of stimuli, the reaction to which had not previously been learned. If a mouse is to succeed in recognizing and reacting appropriately towards a cat it must do so the first time or not at all, and it cannot afford to make the mistake of recognizing black cats as cats but not white ones. The nervous system has solved this problem in what would seem to be the only possible way: it has introduced plasticity into the receptive side so that what the animal reacts to is not a mosaic of all the individual features of the object perceived, but a pattern which constitutes an abstraction from any particular individual, but for that very reason is common to all individuals of the group. Thus, for example, a rat can be trained to recognize, in the sense of reacting in a trained manner to, triangles as distinct from other geometrical figures.

In this connexion pattern is a general term of wide application and it usually stands for something much more complex than the instances which we have just considered. Thus, visual patterns may take into account not merely outline but also light and shade and movement, and patterns can be discovered by other senses than vision: a musical tune, for example, is a pattern which is extended in time and which remains the same whatever its key and whatever the instrument on which it is played. As I have pointed out (Brain, 1950) the recognition of words in speech involves an identical physiological process. We recognize a pattern which underlies all the auditory stimuli

involved in uttering a particular word, though from a physical point of view and even from the point of view of stimuli which they produce in the auditory cortex they must in most respects be different from one another. In the same way we recognize some common patterns in all the visual representations of a single word. And in man we can take the process much further, for not only is there such a pattern through which we recognize a word we hear and another pattern through which we recognize a word we see, but these in turn must submit to a similar process at a higher level by which we reach a conception of the word as an element in thought and words again are grouped into the patterns which constitute sentences which underlie propositional speech, and it would seem that abstract thought itself need only involve the same physiological process at a higher level and in greater complexity.

The Cerebral Basis of Feeling

The link between feeling and representation is reflected in the impossibility of making a complete physiological and anatomical distinction between the functions of the cortex and those of the diencephalon. Nevertheless, I think that Head and Holmes (1920) were right in maintaining that the conscious experiences which we call feelings are correlated with the diencephalic nuclei, particularly the optic thalamus, in the sense that we experience feelings when nervous impulses reach these parts of the brain.

Is the localization of pain a function of the optic thalamus? The experimental work of Dusser de Barenne (1935) has revealed a previously unsuspected intricacy in the thalamus including the bilateral representation of cutaneous sensation in each thalamus, and points to what he calls "the high level of functional integration attained in thalamic activity". It seems likely that a considerable degree of pain-localization occurs in the thalamus though the sensory cortex probably contributes greatly to the accuracy with which the site of the painful stimulus is recognized.

The Biology of Consciousness

Whether or not the behaviour of any organism which possesses a nervous system can be explained entirely in terms of reflex action, there can be no doubt that organisms with the most primitive types of nervous system exhibit mainly the characteristics which we have come to associate with the simpler types of reflex action, similar in essentials to those studied by Sherrington in the spinal cord of the dog. Of these I would stress two. The first is the inevitability or automaticity of response. This, of course, does not mean that the same stimulus always produces exactly the same effect, for the response is modified by the state of the rest of the nervous system at the time at which it is applied, but within these limits the response to the stimulus is automatic. Secondly, both the stimulus and the response are immediate. When we think of such reflexes we picture some kind of stimulus applied directly to the organism, as when salivation is produced by placing meat in a dog's mouth, or the orbicularis oculi contracts on touching the cornea. It is only in the more highly evolved animals that distance-receptors come to assume importance as reflex channels. In the case of the primitive reflex in the primitive organism the stimulus is immediate in the sense that it is not mediated, that is, it is a direct contact with some part of the animal's body. The response is similarly immediate or practically so: there is no long delay between the arrival of the stimulus and the reaction of the effector organ, and it is clear that consciousness could add nothing to a reaction which is the inevitable response to a stimulus.

One of the great advances in evolution was the development of what Sherrington (1947) has called distance-receptors, that is, the receptors reacting to objects at a

distance. The development of distance-receptors had a profound effect upon the organism's relationship not only to space but also to time. If it is to react to objects at a distance, time must enter into the organization of its nervous system in a manner which has no parallel in the more primitive creature which responds automatically to immediate stimuli. The organism which is to react to an object at a distance must initiate a course of action which takes time, whether it is to go in pursuit of it or endeavour to avoid it. No doubt in the lowliest organisms with distance-receptors the times concerned are not very long. Nevertheless, as soon as reactions evolved were organized in time and directed towards objects continuing in time, the nervous system came to possess potentially a type of reaction which was capable of maintaining a specific activity for an indefinitely extended length of time.

How was this done? By the development of new types of nervous function, which, though we consider them separately, are so closely integrated in action that their separation is to some extent an artificial abstraction. The first is feeling, which provides the motive power which sustains our courses of action in time. The time concerned may be short, as when hunger sends us in search of a meal, or indefinitely protracted as when an interest in scientific research determines the activities of a lifetime.

But, feeling is directed towards an object, and if actions are to take time the organism must possess an enduring representation of that object, and here we reach the other new function of the nervous system, the representation of the external world. I do not propose to discuss the philosophical aspects of consciousness, but probably most, if not all, neurologists accept what has been called "physiological idealism". All that we know about the physiology of the conduction of nervous impulses teaches us that perception only occurs when nervous impulses reach the appropriate end-stations in the brain, that these nervous impulses are all much alike and that they are quite unlike the physical stimuli whether of light, sound or chemical character which initiate them. Our perceptions, therefore, are largely a product of the activity of our nervous system and they are, as we say, "projected", and perceived as being external to ourselves.

As soon as the nervous system had acquired the power to create representations of the external world the potentiality of memory made its appearance. Learning is within the capacity of extremely primitive organisms and it is certainly possible that it may occur in the absence of any representation of the external world, by some process of facilitation of repeated reactions, but it seems impossible that we should remember something of which we have not previously experienced a representation.

If all perception is a symbolic representation it follows that symbolization is an inherent function of the nervous system, and there is no difficulty in understanding the further step by which a hierarchy of symbolic processes occurs. Thus, all speech and thought which employ symbols to represent perceptual experiences or ideas are merely a further development of the symbolic function of the nervous system.

The Nature of Unconsciousness

"Unconscious" is a purely negative term: there is no such *thing* as unconsciousness, and the lesions or disorders of function which abolish consciousness may well be of different kinds. As Jefferson (1944) says "we need to define unconsciousness, whether traumatic or otherwise, by a new term which designates more pointedly its nature, its pathological status in terms of neurophysiology". If we were to attempt to do this, even in the present state of our knowledge, we should find that several such terms were needed. Even clinical observation alone shows that unconscious patients differ from each other profoundly, a point with which we are all familiar. Not only do they vary in respect of such content of consciousness as may remain, but also in

respect of muscle tone, posture, the movements of which they are still capable, the condition of the autonomic nervous system and in many other features. The patient who in an attack of *petit mal* continues to ride a bicycle is in a very different condition from a patient who lies in bed comatose from a lesion in the posterior hypothalamus. To say that both are unconscious is a half-truth which may stifle further enquiry.

Penfield and Jasper (1947) have pointed out that whereas the removal of the anterior frontal region has no effect upon consciousness, seizures beginning there abolish it from the very onset, and Jasper and Droogleever-Fortuyn (1947) claim to have reproduced experimentally the electrical phenomena of *petit mal* in cats by stimulating the intralaminar region of the thalamus. Quite different are the states of so-called hypersomnia produced by lesions of the posterior hypothalamus and I agree with Jefferson (1944) that it is desirable to use a term—he has suggested parasomnia—which indicates that this state both resembles and in important aspects differs from normal sleep. Finally both Jefferson and Cairns (1949) have pointed out that unconsciousness may be produced by lesions occupying the posterior fossa and in Atkinson's (1949) account of the symptoms of thrombosis of the anterior inferior cerebellar artery he mentioned unconsciousness or obscuration of consciousness.

In such cases all the evidence suggests that consciousness is impaired primarily as a result of disturbance of function of the brain-stem rather than of any remote effect upon the supratentorial structures. Various suggestions have been made as to the mechanism of the loss of consciousness in some of these cases (Grey Walter, 1947; Martin, 1949; Williams, 1950). We have still much to learn here, but it looks as though we could already distinguish at least three neurophysiological types of disturbance: (1) *petit mal* dysrhythmia, possibly associated with a discharge from the medial portion of the thalamus; (2) parasomnia with the disturbance in the posterior hypothalamic region; and (3) a lower brain-stem disorder which, when it is more fully understood, may perhaps throw light upon syncope. There must, of course, be others. Descartes said: "I think, therefore I am," but only a philosopher, surely, would identify thought with existence. As neurologists we should not be surprised that consciousness is most intimately linked with those basal nuclei which made their appearance in the course of evolution millions of years before thought became possible, and since the days of our earliest vertebrate ancestors have sustained the life of the feelings.

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Section of the History of Medicine

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[*October* 4, 1950]

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PRESIDENT'S ADDRESS

By LILIAN LINDSAY, C.B.E., LL.D.Ed., L.D.S.Ed.

OF the many medical men associated with Dr. Samuel Johnson, one of the most fantastic, whimsical, pretentious, research-minded, nebulous and on that account interesting was Sir John Floyer, by whose advice the boy Samuel Johnson was carried to London to be touched for "the evil" by Queen Anne. Of whom Johnson wrote, "A man so conspicuous because he corrupted, perhaps between seventy and eighty, the register, so as to pass for younger than he was". An examination of the register of Hints in Staffordshire, brings to light certain corrections and additions in those parts of the lists of births, marriages and deaths, which concern the Flyer or Floyer family. There is some evidence, taken in conjunction with contemporary literature, of an hereditary foible in the Floyer family, as well as proof of the birth throes of a new class, the so-called upper middle class, and the resentment of the older landed gentry at encroachment on their privileges.

In 1617, Fynes Morryson wrote "Gentlemen dysdain traffic, thinking it to abase gentry." And in 1669—Sir Simon Degge wrote to Mr. Digby deploring the changes in estates "not by marriages as heretofore but by purchase". The landlords were spending their substance in riotous living in London and mortgaging their country estates to pay their debts. "Since by country trades in this late age many are crept into handsome estates, Mr. Floyer of Hints's grandfather was a mercer in Uttoxeter". This grandfather was a certain Richard Floyer, son of Thomas who came from Devonshire to Uttoxeter and started trade there. Richard, his son, joined in the business and prospered. With the profits so gained he bought one mortgage after another and literally crept into a handsome estate. He went so far as to hint at a coat of arms. He received public reproof at the visitation of Staffordshire in 1584 when "ignobilis" was written after his name. He was put on the list of those "who before time had called, and written themselves gentlemen of which there is no proof, and they are so disclaimed in the chief parts of the hundreds wherein they dwell".

Richard, however, determined that his son should be educated as a gentleman and Ralph son of Richard was entered as a barrister of the Middle Temple.

Ralph Floyer bought the Manor House, Hints Hall, in 1600 and in 1603 his son, Richard, was born. In the register after Ralph's name a later hand has added the word "Gent" every time the name appears.

In 1638, Richard Floyer, born in 1603, married Elizabeth Babington. In 1646 their first child and heir Matthew was born. In 1647 a second child and daughter Elizabeth was born and in 1649 their third child and second son John was born.

There is an alteration after this entry but as it is from the 25th of April to the 3rd of March it makes him over a month older instead of younger.

Is it possible that the great Samuel Johnson was repeating idle gossip without proof?

In 1678 Richard Floyer died and there is another addition by a later hand—"Lord of the Manor of Hints".

In 1661 there is an interesting entry in the register "Since it doth evidently appear unto me Thomas Brookes curate of this parish of Hints that Elizabeth Flyer wife of Richard Flyer Esq. hath need of licence to eat flesh by reason of her sickness which is notorious, I do therefore by the authority to me given by the statute on that behalf made, give licence to her the said Elizabeth to eat flesh during the time of her said sickness,—and permits to have it made redy and dressed in ye said Flyer's house at Hints for her. Witness my hand the 5th day of March 1661".

This was evidently in Lent. The statute mentioned was the 5th of Elizabeth enforcing abstinence from eating flesh in Lent and on certain Saints' days—"to promote fisheries maintain mariners and set men a-fishing" (Mackenzie, E. C., Sacred Archæology, 1868). It was dispensed by licences which were sold according to the rank of the applicants by curates. This was equivalent to a doctor's certificate in a time of rationing.

In 1661 the name of Floyer appears in the records of Lichfield when Mrs. Floyer sub-

Sr John Floyer Kt

1649–1734

A line drawing found by Professor J. A. Gunn loose in a copy of Harwood's "History and Antiquities of the Church and City of Lichfield" in the Bodleian Library.

subscribed £5 to the fund for restoring the cathedral wrecked by the armies of the Parliament. Great were the activities—the King gave "100 fair timber trees" and the good bishop Hacket £1,683 14s. 3d. He roused his servants and with hired teams he laid the first hand to the pious work. Young John Floyer would be 12 years of age at that time and doubtless took part in these doings. He would hear stories of the King martyred in the year of his birth 1649.

There is no mention of John Floyer in the list of scholars at Lichfield Grammar School. It is probable that being son of the Lord of the Manor, he would have had a private tutor—in any case he matriculated at Queen's College, Oxford, at the age of 15 in 1664.

As a younger son he would have to choose a profession and John Floyer chose medicine. This meant a course lasting from twelve to fourteen years. It consisted in reading the classics, memorizing the aphorisms of Hippocrates, attending lectures, writing theses and defending them in disputations, but there was no clinical experience, which was denounced by Clowes, sergeant surgeon to Queen Elizabeth as "knowledge without practice winneth the physician small credit of his patient".

Floyer graduated B.A. in 1668, M.A. in 1671, M.B. in 1674, M.D. in 1686.

In 1687 his first book appeared "The Touchstone of Medicines, discovering the virtues of plants, minerals and animals by their Tastes and Smells".

Floyer apologizes for writing in English. He wishes to encourage the study of native or spontaneous plants. The book was printed for Michael Johnson. This has been regarded as proof that Johnson was publisher as well as bookseller.

What were the relations between Floyer and Johnson? It would appear that these were political rather than professional for Floyer was never Johnson's physician. Johnson was a staunch High Churchman and Royalist. He was a scholar—"he propagates learning all over the diocese—all the clergy are his pupils, even the lawyers pick his brains".

At one time Johnson had been well to do, but unfortunate speculations in parchment had reduced his means. It may be that Johnson at one time had performed some service for Floyer, and Floyer being a man of substance had defrayed the expenses of printing his work appending Johnson's name so that he might reap the benefit. It is certain that in 1686 Floyer was involved in the intrigues of James II to get the city of Lichfield into his power, as he had done with other cities. Lichfield was compelled to surrender her charter and accept a new one giving the King power to appoint and remove officers at his will.

A mayor and twelve aldermen were appointed and two justices of the peace, Sir John Floyer and Thomas Hammond. Sir John was appointed for life and after his death a discreet man was to be chosen from among the aldermen who had been appointed and were of the right politics. It was in that year that James II visited Lichfield. He was met by a procession headed by the mayor and steward, who made a speech, and the two justices of the peace. The next day the king touched for the evil in the cathedral. It is noteworthy that the applicants were examined and the certificates signed by the cathedral authorities, not by Floyer, which suggests that he was not recognized as a medical man on that occasion.

"The Touchstone of Medicines" gives autobiographical information. In the preface Floyer speaks of "his late desperate sickness his recovery from which, since he himself has reaped the benefit of his own art, let it be the good wishes of the sons of the art of all good men, that he may long survive his danger". The advertisement adds to this "that he may have the satisfaction and the rest of the world the advantages of his great learning, skill and industry".

This sickness was probably asthma from which he suffered all his life; as Johnson expressed it he "panted on till ninety".

Floyer speaks of his visits to the Apothecaries' "Chelsea Garden" which he says, he could only visit twice on account of affairs. This would be in 1686 when he was knighted. Was he once more involved in intrigue? The Company were forced by James II to surrender their charter granted by James I in 1617. All the officers were removed—even the clerk, who had been a faithful servant for many years, was dismissed in spite of pleadings.

New officers were installed and the Company put under the control of the Attorney-General.

These servile officers presented the king with an address of thanks for his "declaration of indulgence". Floyer speaks of the "ingenious and obliging Mr. Watts". Mr. Watts was a notable character who had been appointed gardener in 1679—chosen from among many applicants for the post. He was an able organizer and gardener. Floyer praises "his ordering of his plants in a method for learners"—a forerunner of the teaching beds in botanical gardens. Also his "artificial heats for the more early ripening of fruits". In the Minutes of the Company mention is made of "payment for garden stoves". Mr. Watts agreed with Floyer as to certain classifications and also as to the tastes of certain plants.

In 1688 the old charter was restored and the old officers reinstated but it was too late. In 1689 there is a note that the ingenious Mr. Watts is missing.

The idea Floyer wishes to convey in this book is that by tasting and smelling the humours of the body and by observation of "the agreements and contrarieties betwixt the tastes of the humours of the body and the taste of the medicine, it was easier for the physician to infer that by a medicine of the same taste the humours of the body might be preserved".

This was the keynote of his practice—preservation for prevention. He said "the prevention of a disease has the same indications as to cure for the cause must be prevented that would produce it". John Hunter also tasted the humours of the body. There is a good deal in common between John Floyer and John Hunter, both had an insatiable curiosity as to the secrets of Nature and a passionate desire to fathom them, with this difference—Floyer was saturated with classical learning which Hunter regarded as effeminate. He ran away from Oxford and stated "They wanted to make an old woman of me. They wanted to stuff me with Greek and Latin but I crushed each project as it arose".

These two men might be taken as types of Cowper's "Wisdom and Knowledge".

"Knowledge dwells in heads replete
with thoughts of other men
Wisdom in heads attentive to their own".

It might form a subject for debate whether an original mind should be left uneducated—for "borrowing dulls the edge of husbandry".

It was the passion for experiment which suggested to Floyer that his friend Johnson should take his son Samuel to London to be "touched" by Queen Anne. He did not examine the applicants at Lichfield in 1686, but here was a child with scrofula and the Queen was touching for the evil; an opportunity not to be missed for discovery of the truth concerning the efficacy of these cures. It was not superstition as Boswell suggested. Incidentally Floyer quotes the Welsh saying that "no child has rickets that has not a dirty slut for a nurse" and it must be remembered that Samuel's nurse was held responsible for his scrofula.

Like Hunter, Floyer experimented on himself for he deprecated those physicians "who caused their patients to swallow what they dared not taste themselves". He admits he has blistered his mouth with some things and disordered his stomach by inadvertently swallowing others, but adds that with caution this could be avoided. He experimented on his man and his dog—a greyhound. This last may have been influenced by the account of experiments conducted by the young scientists a quarter of a century earlier at Oxford. Unlike Christopher Wren Floyer gave the dog drugs between pieces of bread and butter, instead of by injection, which had little or no effect "so strong are the spirits of dogs in resisting opiates". A cake of nux vomica produced "convulsions and shortness of breath" but "he soon recovered". Thirty berries of solanum lignosum were administered after which "he presently run mad and died". "I found the same in his stomach." The rest of the book is like Culpepper's Complete Herbal without the astrology.

Nine years elapsed before another work appeared. It has been suggested that Floyer may have been engaged in the intrigue of James II in Ireland but so far there is no proof of this.

In 1697 appeared "The History of Cold Baths" dedicated to the Duke of Devonshire in which the waters of Buxton and Matlock receive praise.

The indefatigable Floyer travelled all over the country visiting all the springs, wells and watering places—analysing the water and performing experiments on himself and others.

His fantastic language finds expression in a description of a case of a woman *in extremis* "The vital spark was even blinking in its socket the soul (one foot over the threshold) leaving its battered and decayed tenement, when by a cautious use of the Bath waters and bitters a new life was put into her lease".

The history begins at the Flood which was the purification of the earth by immersion—a most interesting quotation from Vitruvius the old Roman architect is given. Vitruvius said that the heat of hot springs was due to a bituminous earth, a profound observation when the hot spring at Bath is considered as rich in radium emanation.

Floyer describes how the physician Musa cured Augustus with cold baths and was rewarded by the order of the Emperor for his statue to be placed next to that of Æsculapius on the Capitol. Floyer adds "he killed Marcellus six months after he cured the emperor by the same treatment improperly applied—this obliged him to be more cautious".

There is more valuable information in the history of the case of Mrs. Piser of Repton in Derbyshire, whose limbs were much swollen by a rheumatism which had lasted four years. "The joints of her elbows, wrists, knees and ankles were very big and knotted and so sore she could not suffer any motion in them. Her fingers were contracted close so that she could not move them nor any other of her limbs. Her hands and arms were distorted into a strange figure by the contraction of the sinews, the rest of her body was lean and she had a short cough which gave me a suspicion of a consumption". "After purging and bleeding she was put in a chair and dipped thrice at each bathing in cold water—after that she was put to bed where she sweat plentifully by the help of warm ale and spirit of hartshorn. After some time she was able to move her limbs". This treatment reminded me of Sir Henry Gauvain's treatment at Hayling Island.

This book has been used in support of cold water cure and cold packs—for Floyer advocated bathing in a shirt, keeping the wet shirt on and dressing afterwards. It has also been used by religious communities in support of immersion at baptism. Floyer added a short discourse in the form of question and answer between a curate and an anxious father—who feared the risk of stripping a delicate infant in the chill atmosphere of the church and

the further shock of dipping in the cold water. But the curate says "who would not let this child endure the short severity of dipping in order that he may obtain these inestimable blessings".

The next year 1698 there appeared the small work on asthma, containing the first description of emphysema of the lungs from a dissection of a broken-winded mare. He was the first to ascribe the spasm of asthma to constriction of the bronchi. "The flatulent cachochymia irritates the heart to stronger pulsations for the excretion of those humours."

"If I compare our bodies to a watch and the spirits to the spring of it, since upon that all its motions must depend, as on the spirits in an animal body, and as it would be absurd when the watch is out of order, to lay all the fault upon the spring since its going false must depend on the wheels and many other contrivances, so in our bodies, tho' the spirits produce all the regular and irregular motions, the irregularity must depend on other organs ill constituted so in our bodies the lungs being depressed the regular respiration becomes a dyspnœa". Johnson's verdict on this book was that it wanted order and was therefore obscure, "and his asthma, I think, not the same as mine".

After another nine years the work appeared which gives Floyer a place, as rightly claimed by Professor J. A. Gunn, among the British Masters of Medicine.[1] This is "The Physician's Pulse Watch" in 1707, dedicated to Queen Anne, a piece of original research. Floyer records how he had tested healthy pulses by the minute by pendulum clocks and common watches until he met with the sea minute glass used in his experiments in cold bathing. Thereupon he had a minute watch constructed in a case to be the more easily carried. This watch resembled that belonging to Captain Cuttle for it was in constant need of regulation. "As my watch does run unequally by my minute glass I hereby regulate it and add 5 or 6 to the numbers told by the glass".

The next procedure was to have made a half-minute watch which needed 4 added to the numbers of the glass. Floyer records the numbers of beats of healthy pulses according to age and sex—to the season or before and after meals. He estimates that there are 1½ lb. of blood to every 20 lb. of body-weight and that 1 oz. of blood flows at each pulse beat.

He asks his readers to deal friendly with him for his mistakes "tho' I be insulted by the ridicule of many learned men as I was at first with my book of Cold Baths". He does not claim anything new: "All I pretend is the discovery of a rule whereby we may know the natural pulse and the excesses and defects from this in diseases". Before the Pulse Watch all was conjecture, "some pulses, they said, had a good rhythmus and some were without rhythmus, but all this is too curious and not useful. These are musical and geometrical notions which were adapted to Physic formerly but not sensible affections on our sense of feeling and therefore must be rejected." "The Hardness does not depend on the Hardness of the Skin of the artery as the old writers supposed but on the fulness or obstruction of the artery in Inflammations and Pains—or constriction of the solid Parts—or any compression by which the circulation is stopped in some Parts."

The experiment with the "Whole Ileon of a Cow" is well known. Floyer laid it in three or four rings on his grass, one end attached to "Sir Sam. Moreland's Hand-Engine" the other nailed to a stool by one edge of the gut. The pump stood in a pail of water.

"The Annular Fibres by their natural restitution promoted the motion of the water, and kept the stream from any interruption, tho' the Injection was made by intervals." When taking the pulse the physician must be healthful, fasting, free from cares and take a reasonable time to feel the pulse in both wrists. He says that Harvey's discovery was expected "to make great and general Innovations into the whole Practice of Physick but it has had no such Effect". Nevertheless Floyer had an admiration for Harvey's work and even admitted that Harvey might have written a useful book on the pulse and was sure from hints in his work "De Motu Cordis" that he meant to write one.

Floyer preferred Galen to Harvey and quotes Galen's explanation of the heart beats—"the flux of the animal spirits along the nerves into the muscular tissue of the heart is the cause of its beating".

At the end of "The Pulse Watch" Floyer records the number of respirations to the minute and compares them with the pulse beats according to age, sex, season, &c. He had extended his knowledge of emphysema and had dissected five broken-winded horses besides crocked hawks and post-mortems of patients. One who had died of a quotidian had "bladders full of air on the lungs". He described also empyema of the lungs in a consumptive whose lungs showed "purulent tuberculæ".

[1]British Masters of Medicine. Chapter by Prof. J. A. Gunn, Publ. by the *Medical Press and Circular*, London, 1936.

He was growing old and his next book was on Galen's work on the health of old men. This could be preserved by fresh air, exercise, regular diet, temperance in all things especially alcohol and tobacco. The asthmatic should avoid damp air, dust and bad smells. He now advocates warm baths, "if they are luxuries why not for health and cleanliness. If the English knew the use of warm baths like the Romans they would have them made in their houses".

Inunctions are good. Floyer had an oil expressed from mustard seed with which he anointed his body after friction with brushes in front of the fire, this was washed off with warm water; "this made me feel fresh and strong and eased the scorbutic itching of the skin". From this it would seem that Sir John suffered from that added affliction of the asthmatic, eczema.

Phineas Fowke, physician to Charles II and to St. Bartholomew's Hospital, was a friend of Floyer who lent him books on asthma at the time when Floyer was writing on that matter. Fowke was a Jacobite and condemned the heads of the Oxford Colleges for their resistance to James II, quoting Seth Ward "They that resist shall receive damnation". Floyer, in a letter thanking Fowke for the books, says that the old authors are the best, they will live being true. Fowke is praised for his wisdom in leaving the pleasures and impertinent business of life in order that he may "the more freely converse with his learned authors".

Floyer decided to follow this example. He published a book on the Epidemics of Hippocrates and another on Sibylline Oracles and the prophecies of Daniel and the Revelation. This last one was dedicated to the Bishop of Lichfield—"Because I am none of your lordship's Clergy I will give this account how I was led into this study of prophecies, I had long considered the Chinese symbols".

These symbols were from the book of medicine Nuy Kim, translated by Sir Henry Wotton. Floyer claims that the Chinese were the first to study the pulse and that they excelled the Greeks. Their theory of the origin of the heart "out of the southern region comes the heat, from it out of fire bitterness, from it the heart is generated, thence the blood, the tongue governs the heart that which is the heaven its colour is red has the sound of laughing the tongue is its window, its vicissitudes are joy and sorrow, its taste is bitterness, its passion joy, too much joy hurts the heart but fear, the passion of the reins which are enemies of the heart conquers joy".

As Floyer justly remarks this is more for poetry and oratory than for medicine. The Asiatics, he says, have a gay and luxurious imagination but the Europeans excel in reasoning and clear expression.

Two of his papers were read before the Royal Society, the dissection of a monstrous pig and one on his old subject the sweet taste of plants.

He married Sarah the daughter of Sir Henry Archbold of Lichfield by whom he had two sons. Her death gave an opportunity for one more evidence of the family foible for it is entered as "The Lady Sarah Floyer wife of Sir John Floyer knight, physician to Charles II and of Lichfield". She was buried in Christ Church, London, April 19, 1732.

I have searched vainly for any mention in the official records of Floyer's appointment as physician to Charles II and this mention in the register of his wife's death is the first reference to it—it occurs once more in the sale of Longdon Hall to "John Floyer Esq., son of Sir John Floyer physician to Charles II".

Sir John died in Lichfield 1734 at the age of 85 having lived through the Commonwealth, five reigns and part of a sixth.

In a letter to Langton, quoted at the beginning of this paper, Johnson wrote "He was not much less than eighty, when to a man of rank who modestly asked his age, he answered, 'Go look' though he was in general a man of civility and elegance".

Floyer's claim to recognition lies, as Professor Gunn points out, in his researches on asthma and the pulse, and, I think, on the emphasis he laid on the preservation of health for he said "Physicians ought to apply themselves with more than ordinary diligence to all the arts of preserving men's lives".

Section of Odontology

President—Sir WILLIAM KELSEY FRY, C.B.E., M.C., M.D.S., F.D.S., M.R.C.S.

[*March* 27, 1950]

President—F. N. DOUBLEDAY, F.D.S., L.R.C.P., M.R.C.S.

Progressive Asymmetry of the Mandible.—C. D. FARRIS, M.R.C.S., L.R.C.P., L.D.S. R.C.S.

Assyrian nurse, aged 27.

History.—Mouth normal in childhood. At age of about 8 years difficult extraction of $\overline{6}|$. Her face was much swollen at the time, and so bruised after it that her grandmother thought her jaw had been broken. (No treatment.) For the past ten years she thinks that her jaw has been getting progressively more asymmetrical, more rapidly so in the last five years, and her friends remark on her changing appearance.

Family history.—Brother has underhung bite. Rest of family normal.

History of previous diseases.—Mastoidectomy, 1929.

Examination.—Dentition: $76|\overline{567}$ missing. Measurement shows left condyle to symphysis greater than right by 2·5 cm. Symphysis is 3 cm. over to right of mid-line, and protruded. Left condyle not markedly enlarged. There is obvious deformity of the face.

The question is whether the deformity is due to overgrowth of the left side or to undergrowth of the right side.

Mrs. D. S. Mountford asked Mr. Farris if in his opinion the asymmetry of the jaw could have had its origin in mechanical causes such as premature extraction of temporary molars causing a cross-bite, or whether it was a pathological overgrowth of bone.

Mr. Farris replied that both he and Professor Rushton believed it was probably an overgrowth of bone.

Paget's Disease Associated with Acromegaly.—C. D. FARRIS, M.R.C.S., L.R.C.P., L.D.S. R.C.S.

Miss K. P., aged 53.

Diagnosis.—(1) Acromegaly—pituitary adenoma. (2) Paget's disease.

History.—Swelling left upper jaw 1942. Increase in size of hands and feet, and obesity. General symptoms of depression, anosmia and polyuria.

Examination.—28.3.47: Typical acromegalic enlargement of hands, feet and lower jaw. Large malar bones, especially on left. Marked enlargement of upper alveolus in the molar regions, especially left, where $|\overline{7}$ is almost covered. Upper and lower incisors show marked separation. Large lipoma on back.

X-ray.—Skull: Changes in vault typical of Paget's disease; enlargement of sella turcica. A.P. distance: 18·3 cm.

Treatment.—8.4.47 to 16.4.47: Deep X-ray to pituitary. Right and left lateral fields 7·5 cm. dia. circular field. Centred with photographic checking. Over-all time eight days; 7 treatments. Total skin dose 2,079 r. Total central dose 1,498 r. The condition improved both locally and generally.

The $|\overline{78}$ were extracted under general anæsthesia. The $|\overline{8}$ was found to be completely ankylosed, the tuberosity of the maxilla came away with it.

31.8.49: $\frac{|\overline{5}}{|\overline{8}}$ extracted under local anæsthesia. $|\overline{5}$ very difficult extraction. Large cementoma on root. Soft bone removed at same time for biopsy; early stages of Paget's disease.

After testosterone 25 mg. I.M.—two injections at three weeks' interval—the bony masses in the jaws and also the hands and feet seemed smaller. Her appearance improved and there was a marked improvement in her mental condition, which has been sustained.

(The case was shown by kind permission of Professor J. S. Mitchell of Addenbrooke's Hospital, Cambridge.)

Histological Changes in a Dentigerous Cyst.—P. A. TOLLER, F.D.S. R.C.S.

12.4.49: A boy of 15 years of age reported with a complaint of periodical pain in a left lower first molar during the last two years.

On examination.—The left lower first molar had been filled but was now badly decayed and broken down. There was obvious swelling over the inner and outer aspects of the ramus and posterior part of the body of the mandible, being fluctuant behind $\lfloor\overline{6}$. The colour of the mucous membrane was normal except over the area of fluctuation where it was bluish. Radiographs showed a large area of rarefaction extending from the anterior root of $\lfloor 6$ backwards and upward to the posterior margin of the ramus. There was a further loculus of rarefaction at the lower border of the mandible beneath the main area, which partly included the misplaced $\lfloor\overline{7}$. $\lfloor\overline{8}$ was not fully formed and was lying near the neck of the condyle.

The appearances were suggestive of a dentigerous cyst involving $\lfloor\overline{7}$, or, alternatively, consistent with an apical cyst involving $\lfloor\overline{6}$ with a smaller dentigerous cyst over $\lfloor 7$. The possibility of adamantinoma could not be excluded.

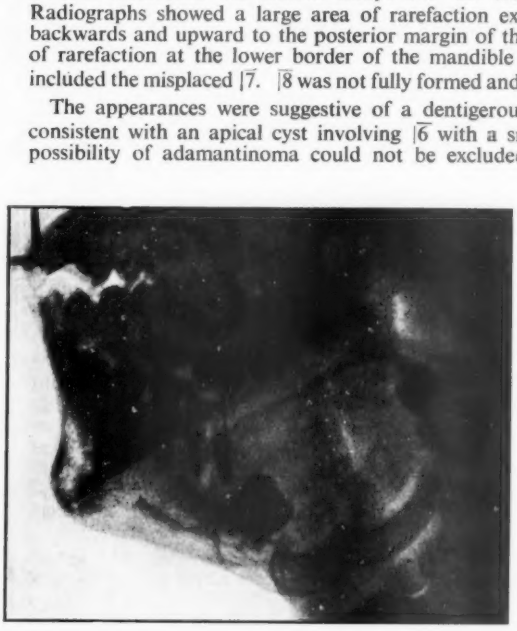

FIG. 1.—Radiograph showing extent of cystic lesion before operation.

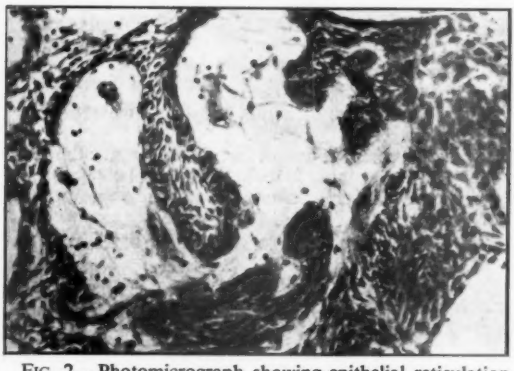

FIG. 2.—Photomicrograph showing epithelial reticulation deep in a myxomatous connective tissue found at the base of the cyst at operation. × 170.

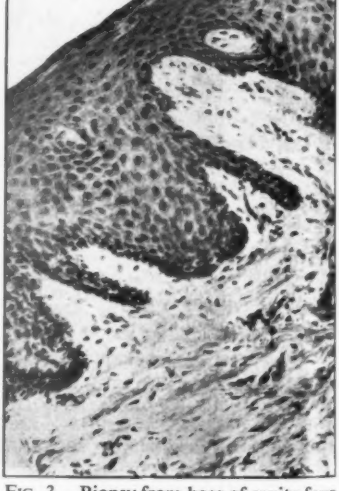

FIG. 3.—Biopsy from base of cavity four months after marsupialization. × 170.

20.4.49: Operation to remove $\lfloor 6$ and roof of cavity from within mouth and to explore cavity. This was found to be cystic with several thick fleshy septa dividing it into two main parts with several smaller incomplete loculi. The walls were of very thick but friable soft tissue, rather red in colour. $\lfloor\overline{7}$ was exposed in upper cavity, but $\lfloor\overline{8}$ entirely covered by lining. Since the appearances were out of keeping with those of a normal epithelial cyst, it was decided to apply a cyst plug pending a biopsy report.

20.5.49: In spite of conflicting opinions in regard to diagnosis, conservative treatment by exteriorization was continued, the original cyst plug being shortened from time to time. The cavity was rapidly filling up from the base but the lining still looked very abnormal.

14.8.49: Cavity further filled up. Second biopsy taken.

14.1.50: Cavity now obliterated to saucer-like depression with second molar lying at its base, but sloping lingually. Plug discarded.

This case is reported in order to show the apparent success of the conservative treatment in spite of unusual histological appearances suggestive of a possible trend toward adamantinoma.

First biopsy report from cyst wall and septa.—There is a massive reticulum of epithelial cells extending irregularly through a very light myxomatous connective tissue base. Fairly vascular. No evidence of inflammatory infiltration. No areas enclosed by the reticulum were cystic other than the main cyst cavities, and there was no cystic breakdown in the epithelial element. The epithelium was squamous but a well defined basal layer was seen in many areas.

This biopsy suggested the possibility of adamantinomatous change.

Second biopsy four months later.—Wall of cyst showed an almost normal epithelial lining on a fibrous tissue base in all areas. No trace of the epithelial reticulum was seen in the deeper tissues.

Relation of Dentigerous Cyst to Adamantinoma

This case brought about an immediate consideration of the possibility of the development of an adamantinoma from a dentigerous cyst as reported by several writers. It also led to a consideration of the use of a conservative method, despite the original biopsy sections.

Relatively few instances of this development have been reported, and a disappointingly high percentage of these reports have either shown no illustrations, or the evidence suggests that a true adamantinoma was present in the first place. For instance, a certain cyst was said to recur as adamantinoma, but since no biopsy of the original cyst was available, this is obviously a useless report. Others show what appears like the flattened lining of a large adamantinoma cavity and compare it with a more typical adamantinomatous area from the same cyst. Churchill (1934), Cahn (1933) and Thoma (1946) have reported cases where adamantinomatous follicles appear truly to have developed from a dentigerous cyst.

The evidence is, however, that such an occurrence must be regarded as *extremely rare*, and in any case likely to be diagnosed by biopsy if doubt exists in cases with an unusual lining.

It would not seem justifiable, therefore, to condemn the very useful conservative operation of exteriorization on the grounds that an adamantinoma may develop from a dentigerous cyst. Some authorities have even advocated complete excision followed by electrocoagulation in all cases of dentigerous cyst. This appears quite unreasonable and unjustifiable. There is no doubt that marsupialization is of great value when the cyst is surgically inaccessible, or in cases where the cyst lies in close relation to an important or delicate structure such as the antrum, or in order to conserve sound teeth in young people by allowing the cyst to fill up and for displaced teeth to migrate back and erupt into a functional position, as first demonstrated by Sprawson.

It is well known that certain cysts, notably maxillary inclusion cysts, fail to respond completely to treatment by marsupialization and the cavity may never become obliterated thereby. If they can be diagnosed as such, these cysts are best enucleated. Others may be exteriorized and maintained open until the cavity is reduced to a more accessible state and until the walls have thickened; then there may secondarily follow a total excision entailing less damage to adjacent structures.

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A Cystic Complex Composite Odontome.—A. E. W. Miles, F.D.S., L.R.C.P., M.R.C.S.

W. M., male, aged 18.

No trouble with teeth and jaws until 4.11.49 when he received a blow on the left side of his jaw. Face became swollen immediately and there was a little difficulty in opening the mouth and some pain on mastication. No bleeding into mouth. The swelling gradually subsided but five days after the injury he began to get severe lancinating pain in left lower jaw.

Presented himself at hospital ten days after the injury. Slight external swelling. No tearing of mucosa and no ecchymosis in floor of mouth. Opening limited but no disturbance of occlusion. Crepitus noticed during examination. Slight fullness of alveolus in region of $\overline{78}$. $\overline{678}$ were missing from the arch. X-rays showed fracture through a dentigerous cyst involving $\overline{8}$ (Fig. 1).

Immobilized for five weeks with cap splints. At end of this time clinical union was present.

2.2.50: Cyst enucleated and ⌈8 removed, the cap splints being retained to provide temporary immobilization.

On section the cyst wall proved to be composed of fibrous tissue with a very thick inner lining of epithelial cells among which there is very little connective tissue stroma. The epithelial cells are of irregular size and shape and are not of basal-cell type. They form whorls or groups and most of the cells at the periphery of the groups are fusiform. Here and there are small collections of columnar cells and in many situations a lumen has developed at the centre of a whorl of cells (Fig. 2). The cells grouped around the lumen form a single layer of high columnar cells with their nuclei at the end of the cell furthest from the lumen. These columnar cells closely resemble ameloblasts, in many cases even to the possession of structures resembling the inner and outer ameloblastic membranes of Leon Williams (Fig. 3). In places the

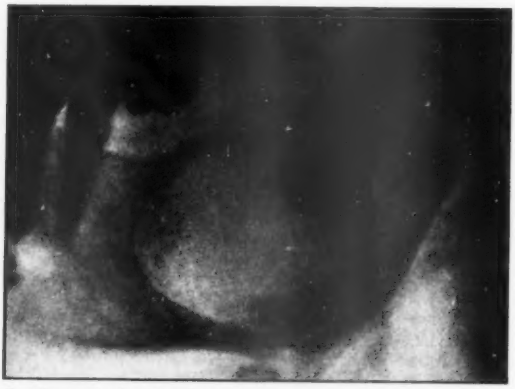

FIG. 1.—Radiograph showing fracture through dentigerous cyst involving ⌈8.

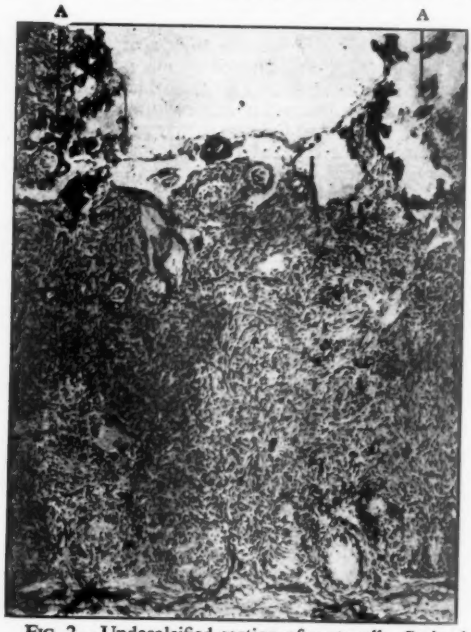

FIG. 2.—Undecalcified section of cyst wall. Stained van Gieson. × 57. A. Fragmented bodies staining mauve.

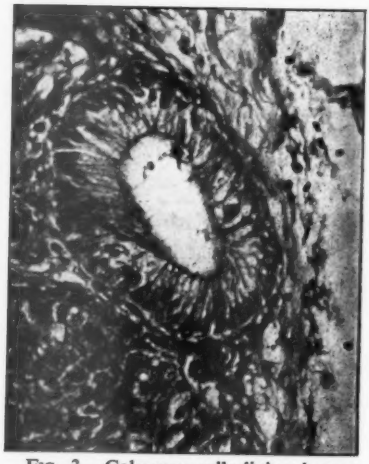

FIG. 3.—Columnar cells lining lumen. Stained hæmatoxylin and eosin. × 225. In other places these cells have laid down enamel matrix which lines the lumen.

lumen is lined by a material which is clearly the product of the columnar cells. It stains, as does developing enamel, yellowish-brown with van Gieson's stain. This staining reaction, together with its relationship to cells resembling ameloblasts, justifies the assumption that the material is enamel matrix, although no prismatic structure can be discerned.

In a few situations the columnar cells or ameloblasts are grouped around a cluster of smaller cells on the surface of which in places is a material of fibrous structure which stains red with van Gieson (Fig. 4). This material intervenes between the central cluster of cells and the ameloblasts or, where it is present, the enamel matrix. Its staining reaction and contiguity to enamel matrix suggest that this material is collagenous dentine matrix. Assuming this to be so, the central cluster of cells must be mesodermal pulp tissue, although it bears only the slightest resemblance to that tissue histologically.

In the superficial and presumably older part of the epithelial lining are a number of irregularly rounded bodies, most of which are structureless but in a few cases show concentric lamination. They stain yellowish-brown with van Gieson but the centres occasionally stain bright red. Some of these bodies have fragmented in the undecalcified sections and the fragmented ones all stain mauve with van Gieson (Fig. 2). The significance of this unusual staining reaction is not clear. No part of developing enamel stains in this way but the enamel matrix of fully developed teeth does sometimes stain with a slightly mauve hue. A test with von Kossa's stain for the presence of calcium in these bodies was negative. Although they apparently represent attempts to form enamel it is curious that in no case are the epithelial cells immediately surrounding these bodies columnar in character.

A large number of sections from various parts of the cyst were examined and finally one larger mass of tissue was found in which tubular dentine could be identified at the centre (Fig. 5). A material which resembles enamel matrix in staining reaction but in which no

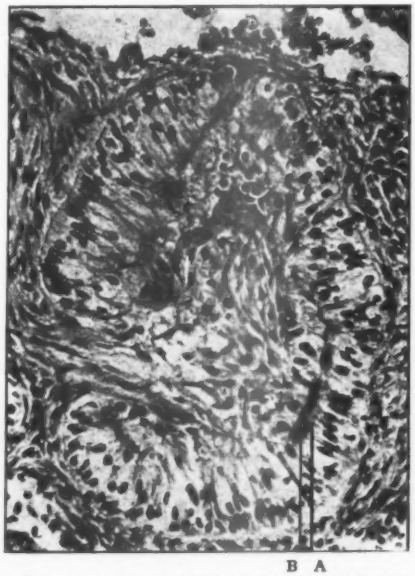

FIG. 4.—A. Enamel matrix staining yellowish-brown. B. Collagenous matrix staining red. × 260. Stained van Gieson.

FIG. 5.—A. Enamel matrix at the periphery. B. Irregular dentine matrix. C. Dentine in which tubules are seen in cross-section. × 320. Stained Mallory's connective tissue stain.

prismatic structure can be discerned forms the periphery of this mass.

Although the epithelium of the lining appears to be invading the fibrous capsule of the cyst, in no place has it been penetrated. The cyst wall in the immediate vicinity of the lower third molar is lined by a thin layer of stratified squamous epithelium.

COMMENTS

At first sight the histology appeared to be that of a multilocular cyst or so-called adamantinoma, but in fact differs from that condition in several respects. The columnar cells are much more like ameloblasts than any cells found in adamantinomas. The orientation of

the columnar cells is also quite different. In adamantinomas the cells which present some slight resemblance to ameloblasts are situated at the periphery of the groups of epithelial cells and if enamel were formed it would be laid down against the connective tissue stroma between the epithelial groups (Fig. 6). In the present case the ameloblasts are situated at the centre of the cell groups, their nuclei are at the opposite poles of the cells from that found in adamantinomas and a material resembling enamel matrix is being deposited within the lumen. It is generally stated that adamantinomas never form enamel but, according to Thoma (1944), it is not uncommon to find a homogeneous zone between the peripheral cells and the stroma which stains yellow with van Gieson and which he regards as abortive enamel formation. The examination of a number of typical adamantinomas has failed to confirm this.

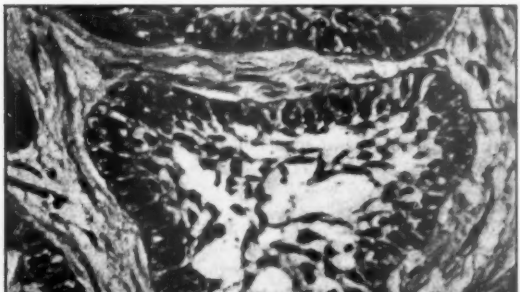

FIG. 6.—Section of a typical adamantinoma from another patient. × 300. Stained hæmatoxylin and eosin. A. Columnar cells orientated towards the surrounding connective tissue.

In a review of the cases of adamantinoma reported in the literature Robinson (1937) found 3 cases in which enamel formation was described and 1 case "in which a substance suggestive of enamel matrix was apparent within the cysts". It has not been possible to trace the case reports to which he refers. The multilocular cyst is not universally accepted as being derived from the epithelial elements of the tooth germ and it has been suggested that the resemblance of its structure to an enamel organ is accidental and superficial. In normal development the formation of enamel is always preceded by the formation of a small amount of dentine and the presence of dentine seems to be necesssary to induce the beginning of enamel matrix formation (Orban, 1944). The supporters of the view that multilocular cysts are derived from dental formative epithelium point out that the dentine papilla is not involved in the pathogenesis and that therefore, in the absence of tissue with the potentiality of forming dentine, it is not possible for the tumour cells to lay down enamel. In the present case, although it is a tumour in which both enamel and dentine are being formed, in many situations in which enamel matrix is present there is no sign of dentine.

The discovery of dentine in this case makes it necessary to place it in the category of complex composite odontomes. The opportunities of examining composite odontomes during their active formative period are very rare. Sprawson and Keizer (1933) have drawn attention to the fact that the histological appearances of a developing composite odontome before any calcification has taken place may exactly resemble those of a multilocular cyst. The question arises whether, if this cyst had been left undisturbed, it would have eventually exhausted its potentiality of forming tooth substance, as is always the case in calcified composite odontomes. The complexity of the resulting calcified mass would have been very great indeed, and, unless the cyst cavity had become encroached upon later by the growth of solid tissue, it would have been very much dilated.

On the other hand the epithelium in this cyst wall possesses a greater degree of disorganization and abnormality of cell forms than one would suppose to have been the case in most calcified complex odontomes, in which, although the arrangement of the tissues is completely disorganized, the tissues themselves are usually of relatively normal structure and it may therefore be assumed that the cells that gave rise to those tissues were not very abnormal in form. The high degree of disorganization of the epithelium in the present case suggests that it may have exhibited unceasing growth, namely forming fragments of enamel and dentine during its career, thus behaving more like the so-called adamantinoma. If so, and supposing the adamantinoma to be truly derived from enamel-forming epithelium, it would provide a link between that condition and the usual type of complex composite odontome.

These questions are difficult to answer in the absence of recorded experience of similar cases. The only similar cases which have been found in the literature are 3 reported by Stafne (1948) as epithelial tumours associated with developmental cysts of the maxilla. The histological appearances of one of these cases in particular are very closely similar, although Stafne makes no reference to any dentine having been recognized in the sections.

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Cervico-facial Actinomycosis.—A. B. MACGREGOR, M.D., F.D.S.

History.—Man aged 50, suffering from cervico-facial actinomycosis. In 1947, following the removal of fifteen lower teeth under general anæthesia, he noticed a number of what appeared to be small boils in the left cheek in the region of the angle of the mandible. These boils burst and periodically reappeared until a large lump formed which forced him to attend hospital. A course of iodides was prescribed, gr. 300 (19½ g.) per day being given over a period of six months. Very little improvement appeared to follow this treatment. On being first seen by the writer the patient was edentulous, with a severe degree of trismus causing difficulty in removing and inserting his dentures. Multiple healed sinuses were present in the left cheek with one abscess under the chin, and a very large fluctuant swelling in the left temporal region. The whole of the left cheek was swollen and hard.

Diagnosis.—The temporal abscess was aspirated and a slide obtained, confirming the diagnosis of actinomycosis.

Treatment.—A course of penicillin, 1,200,000 units a day was given over a period of five weeks. In addition the temporal abscess was aspirated while pus remained and replaced with penicillin.

No untoward results were seen following the prolonged administration of penicillin. The trismus gradually decreased and the hard swelling in the left cheek became softer until, at the end of six weeks, he had almost full opening of the jaw and all sinuses were healed, as were the abscesses. He returned home and no recurrence has been noted to December 1950.

Note.—Numerous other cases have been treated with local and general penicillin, which appears to be extremely successful in combating the disease, though it seems certain that numerous strains of the organism exist, some proving more refractory to treatment than others.

Apical Resorption.—F. FRASER, L.D.S.

Woman, aged 30, first seen during May, 1949, following an accidental blow, whilst unwell in bed, which had partially dislocated |1.

The clinical condition of the mouth presented the usual picture associated with the mouth-breather: a high narrow arch with prominent, somewhat fan-shaped upper incisors; lower incisors taller than their neighbours and occluding almost against the palatal gingivæ; poor paradental condition, and teeth in general none too firm. An acrylic splint was fitted and maintained in position for between two and three weeks, when it was found that the tooth had sufficiently tightened for treatment to be discontinued.

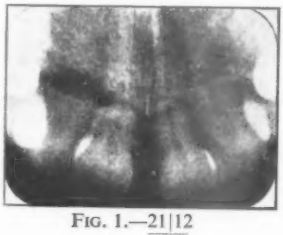

FIG. 1.—21|12

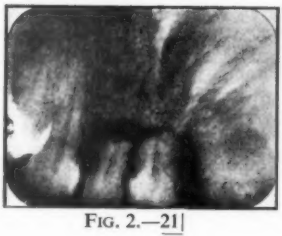

FIG. 2.—21|

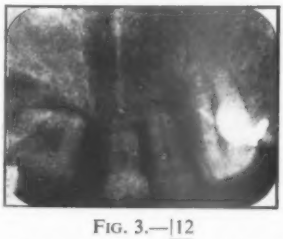

FIG. 3.—|12

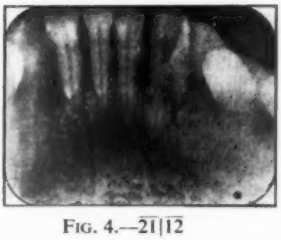

FIG. 4.—21|12

No radiographs were taken at this time as no abnormality was suspected, and the patient was seen at her home.

In March 1950 the patient attended again and reported a further similar mishap which had loosened 2|.

On examination 2| was so loose as to appear to have been fractured away from its root. It was accordingly radiographed, when it was discovered that the root was entirely absent, and, further, that the other three upper incisors were similarly affected (Figs. 1, 2 and 3).

Examination of the lower incisors showed $\overline{2}|$ also to have its root completely resorbed. $\overline{1}|$ has partial resorption with "necking-in" of the root, the condition tailing off in the remaining incisors (Fig. 4). No other teeth appear to be affected.

All the teeth have vital pulps responding normally to thermal changes with the exception of $|\underline{1}$, which has reduced vitality and is somewhat darkened in colour.

In view of the connexion thought to exist between apical resorption and long-continued trauma the patient was questioned in regard to orthodontic treatment during youth, and gave a history of such treatment extending over two to three years, but confined exclusively to the upper jaw.

Mixed Salivary Tumour of Palate.—B. W. FICKLING, F.R.C.S., F.D.S.

G. H., male, aged 40.

1942: Many teeth extracted. Dentures fitted.

1944: First noticed swelling in palate. Operation under local anæsthetic—grumous debris curetted.

21.9.44: Attended R.A.F. Hospital Uxbridge. Semifluctuant swelling 2 × 2 cm. at back of hard palate. X-ray revealed nothing abnormal.

27.9.44: *Operation* under general anæsthesia. No pus found, pieces of hardish tissue enucleated. Cavity packed.

Pathological report. — Mixed salivary tumour.

2.5.45: Several follow-up examinations. No abnormality noted.

June 1949: Slight swelling apparent again.

10.8.49: Attended Plastic and Jaw Centre, Hill End Hospital. Slight domed swelling over right posterior palatine foramen. 2–3 cm. across, fluctuant. Mucous membrane normal.

28.9.49: Excision of portion of palate and enucleation of tumour. Descending palatine vessels tied. Small opening into right antrum. Sutured with small thrombin pack.

Pathological report.—Infiltrating growth consisting of cells arranged in cords and sheets with only little tendency to acinous formation. The cells are embedded in a mucinous matrix. Mixed salivary tumour (Fig. 1).

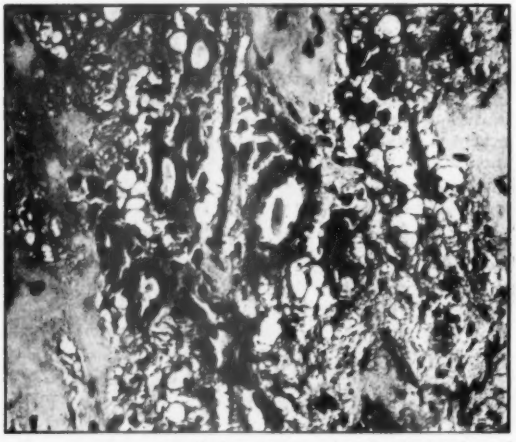

FIG. 1.—Tumour cells in a stroma showing hydropic and mucoid degeneration. Attempt at cell-nest formation in centre of field. × 125.

14.10.49: Consultation re radiotherapy.

Professor W. B. Windeyer and Dr. R. Ward report: "Mixed salivary tumours are comparatively radio-resistant . . . we often give pre-operative irradiation . . . if there should be recurrence . . . discuss the question of radiation with further operation."

20.9.50: No evidence of change since operation.

Osteoma of Mandible.—B. W. FICKLING, F.R.C.S., F.D.S.

V. P., female, aged 37.

Since her 'teens has had a lump at the back of the left lower jaw within the mouth. Teeth in this area were extracted in her 'teens. Upper teeth extracted and upper denture fitted nine years ago. Lump caused no comment then.

March 1950: Now has a bruised feeling in the jaw. No marked pain. No bleeding. No anæsthesia.

On examination.—Hard rounded swelling of jaw in $|\overline{8}$ region with indentation of teeth of upper denture. Some external swelling.

X-ray.—Ovoid radio-opaque area 4 × 3 cm. in the molar region of the mandible and extending lingually. Homogeneous bone pattern of cancellous nature. No line of demarcation can be observed.

16.8.50: Operation for removal by extra-oral approach.

Pathological report.—Macroscopic description: Specimen consists of two fragments of bone which have been sectioned prior to receipt.

Histological report.—Section shows these fragments to consist of closely packed bony lamellæ, very irregular in shape and arrangement, and separated by vascular fibrous tissue. Active bone formation is still apparent. Appearances are those of an osteoma.

[*April* 24, 1950]

A Case of Complete Cemental Metaplasia of the Dental Pulp.—Professor A. I. DARLING, M.R.C.S., L.R.C.P., F.D.S. R.C.S.

In the course of routine histological examination of a series of ground sections, a mandibular incisor was found with its pulp chamber completely occluded by cementum. The section was cut longitudinally through the tooth in a mesio-distal plane. It shows evidence of considerable incisal attrition and a suggestion of early caries or precarious decalcification of one enamel surface. The dentine appears to be normal though the apex of the root has been lost in grinding.

The pulp chamber and root canals are of normal form, showing no evidence of secondary dentine nor of any previous pulpal disease. There is no soft tissue in any part of the pulpal area, which is completely occupied by a mass of calcified tissue. (Fig. 1). Throughout this calcified mass typical spider-like cemental lacunæ and canaliculæ can be seen (Fig. 2). These

FIG. 1.

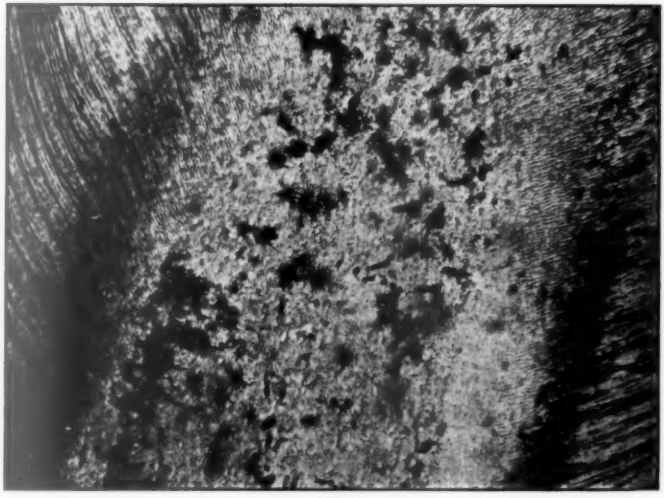

FIG. 2.

FIG. 1.—Ground section of lower incisor in mesiodistal longitudinal plane showing hard tissue occupying the pulp chamber and root canal. × 2½.

FIG. 2.—Enlargement of a portion of Fig. 1, showing coronal part of pulp chamber filled with cementum. × 100.

are not arranged in any particular pattern nor are they evenly distributed. The majority are to be found in the occlusal third of the pulp cavity. The form of the lacunæ and the absence of haversian systems confirm the view that the tissue replacing the pulp is cementum.

It is regretted that nothing is known of the history of the tooth except that it was one of several teeth extracted from an adult patient. None of the other teeth shows any abnormality of the pulp.

Cementum has frequently been demonstrated covering the pulpal surfaces of the dentine for a short distance from the apical foramen (Salter, 1874; Hopewell-Smith, 1903; Davis, 1923; Kronfeld, 1949). More rarely it has been shown forming a thin lining to the whole of the pulp chamber and root canal (Kronfeld, 1949), while Euler (1921) has recorded a case in which the coronal pulp but not the root canals was filled with cementum. No record of complete obliteration of the dental pulp by cementum has been found in the literature.

Calcification of the pulp occurs commonly in the form of pulp stones or diffuse areas of calcific degeneration. These are mostly amorphous deposits of calcium salts in areas of degeneration and are probably the result of mild degrees of chronic irritation or possibly of senile degeneration. Less commonly pulp stones are found showing the structure of tubular dentine with associated odontoblasts. It is presumed that these odontoblasts have differentiated from the fibroblasts normally present within the pulp and that the organizing influence which stimulates this differentiation may be the presence of epithelial rests within the pulp.

Cementum and bone are normally formed by the cells of the dental follicle and its successor, the periodontal membrane. It is believed that the cementoblasts and osteoblasts are derived from the fibroblasts of the dental follicle. The formation of new cementum in productive periodontitis shows that periodontal fibroblasts retain their powers of differentiation after the tooth is fully developed.

There appears to be a marked difference between the organizing influences at work within the pulp which may produce odontoblasts from fibroblasts and those working in the periodontal membrane which produce cementoblasts from apparently similar fibroblasts.

When cementum is found lining the pulpal surfaces of the apical foramen and extending for a short distance into the pulp canal it is presumed that the cementoblasts responsible for its formation have migrated to these sites from the closely related periodontal membrane (Hopewell-Smith, 1903: Euler, 1921; Grove, 1921; Davis, 1923; Kronfeld, 1949), but this is much less satisfactory as an explanation of complete occlusion of the pulp by cementum.

Euler (1921) has described a third molar in which the cementum laid down in the coronal pulp was separated from the periodontal membrane by atrophic pulp tissue in the root canals. From this he deduced that there had been a disturbance of metabolism in the coronal pulp resulting in the production of cementum instead of dentine. This he calls metaplasia. Euler's case is similar to the case described in every respect except that in this case the root canal is also filled with cementum.

In both cases the junction between dentine and cementum shows no evidence of dentinal resorption but suggests that the deposition of calcified tissue has been more or less continuous though the type of tissue has changed. There is no evidence of disease, other than early decalcification of the enamel, and one can only presume that the organizing influences within the pulp have been modified so that they approximate more closely to those at work within the periodontal membrane thus causing a transformation of odontoblasts into cementoblasts or, more probably, a replacement of odontoblasts by cementoblasts derived from the fibroblasts of the pulp. Such a condition is metaplasia and the case is therefore one of complete cemental metaplasia of the dental pulp, with no evidence to show the cause of the condition.

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[*May* 22, 1950]

MEETING HELD AT THE ROYAL COLLEGE OF SURGEONS, LONDON

A Rare Displacement of a Canine in a Tiger.—Sir FRANK COLYER, K.B.E., LL.D., F.R.C.S.

The skull of an Indian Tiger (*Panthera tigris tigris*) showing a remarkable displacement of the right maxillary canine has recently been presented to the Museum of the Royal College of Surgeons. The animal was shot by Lt.-Col. R. C. Crowdy in the U.P. forests of India, near Hardwar, March 1947.

The main portion of the canine, as shown in Fig. 1, is situated in an oblique direction across the right nasal fossa, the crown having pierced the hard palate as seen in Fig. 2. The end of the root of the canine is embedded in a mass of new bone on the outer aspect of the nasal fossa, the septum being deviated towards the left. The injured tooth, as shown in Fig. 3, has a necrotic appearance and is smaller than the left tooth.

In the view of the palate, Fig. 2, there are three features to which attention may be drawn as they shed light on the nature and time of the injury. The first is that a flake has been split off the crown of the tooth, exposing the pulp cavity. At the top right-hand side there is a fissure through the dentine and enamel; this fissure, which passes in a longitudinal direction up the root, was caused by the injury. The fissures running in transverse and oblique directions are artefacts, the result of the specimen drying. When received, there was a small amount of loose hair in the pulp cavity. The margin of the enamel surrounding the fractured surface

is crossed by a series of fine grooves produced by the action of the animal's tongue. The second feature is the condition of the empty socket of the canine. It is evident from its small size that it was not occupied by a fully erupted permanent tooth. If it had been occupied by a partly erupted permanent tooth then the injury would have occurred after the eruption of the second premolar, as this tooth in the Felidæ appears soon after the deciduous dentition is in position. There are, however, no signs of injury to the bone around the tooth except on the anterior aspect where it forms part of the septum between the premolar and the canine.

FIG. 1.

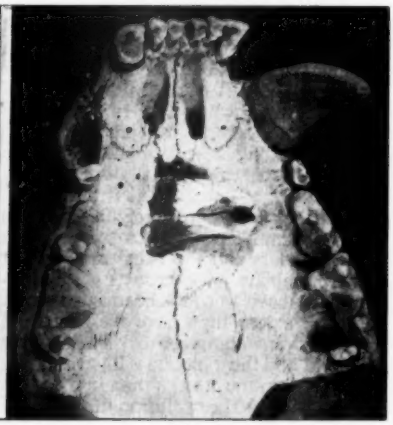

FIG. 2.

FIG. 3.

FIG. 1.—*Panthera tigris tigris* (Linnæus). The Indian Tiger. Skull showing displacement of the right canine. Royal College of Surgeons' Museum, Odont. Sect. G.98.111.

FIG. 2.—Palatal view of the skull shown in Fig. 1.

FIG. 3.—Views of the injured and the normal canines of the specimen shown in Fig. 1.

The empty socket on the other hand is too large for a deciduous tooth but not larger than would result from the avulsion of the tooth in an outward direction. The third feature is the abnormal position of the second premolar. It is possible that this may be due to the tooth-bud having been given off from the tooth-band in an abnormal position, but from the fact that the variation is associated with injury it is more likely that it was the result of trauma. As already stated the condition of the bone seems to preclude injury after eruption and it is therefore probable that the abnormality resulted from injury to the tooth in the crypt, and that would be before the eruption of the permanent canine.

From the evidence afforded by the specimen I think the chain of events was as follows: A severe injury to the deciduous canine led to loss of that tooth and the displacement of the forming second premolar. The upward impact of the deciduous tooth on the permanent tooth spilt a flake off the crown of the latter and dislocated it into the nasal fossa, where the crown came in contact with the floor of the fossa but still retained a hold on the bone around the apical portion of the root. The growth around the end of the root exerted pressure upon the floor of the fossa and gradually led to absorption of the bone and the appearance of the crown in the mouth, where it must have been an unwelcome visitor to the animal and hence its constant efforts to remove it by the tongue.

The tiger according to the donor was in perfect condition and measured 9 ft. 10 in. (3 m.) between pegs; it was a notorious cattle raider but was not, as far as was known, a man-eater.

Asymmetry of the Dental Arch in a Toque Monkey *(Macaca sinica)*.—Sir FRANK COLYER, K.B.E., LL.D., F.R.C.S.

Asymmetry of the dental arch in monkeys is uncommon but not rare and in some cases is associated with considerable distortion of the facial portion of the skull. In a few of the specimens showing the abnormality there is evidence of injury to teeth or to the bones; in the majority, however, the cause is hidden in obscurity. The following case in a Toque monkey (*Macaca sinica*) is worthy of record as it is associated with early loss of the right maxillary first permanent molar.

The specimen shows plainly a distinct flattening of the right side of the facial skeleton, the anterior parts of both maxillæ being deflected slightly to the right. The left canine, premolars and molars, as shown in Fig. 1, are situated more anteriorly in the jaws than the corresponding teeth of the opposite side. The space originally occupied by the lost right maxillary first permanent molar has been completely filled by the forward movement of the second and third molars and the backward drift of the premolars. The crowns of the premolars have moved backwards to a greater extent than have the roots and the forward compensatory shift of the second and third molars is likewise more apparent in the crowns than in the roots of the teeth. The occlusion of the molar teeth on the right side is abnormal, the maxillary teeth being well in advance of their normal relationship with the mandibular. Unfortunately, the mandibular right first molar and second premolar have been lost from the specimen but it is evident that there were two large "food pockets" between the first and second molars and the second and third respectively.

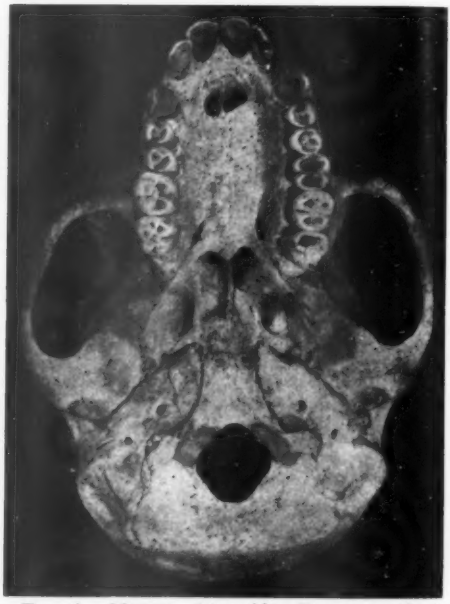

FIG. 1.—*Macaca sinica* (the Toque monkey). Female. Polgahwela, Ceylon. A skull showing marked asymmetry of the dental arch. Royal College of Surgeons' Museum, Odont. Sect. G.8.2.

In the norma basilaris the area enclosed between the zygomatic arch and the skull wall is much smaller on the right than on the left: the right sphenomaxillary fissure is distinctly narrower than its fellow, due apparently to the backward drift of the right maxilla. The right alisphenoid is perhaps better developed than the left.

The left posterior palatine foramina are distinctly larger than, and are situated slightly forward to, those of the right side: the inferior rim of the right orbit descends to a lower level than that of the left, and the distance between it and the alveolar margin is less than the contralateral measurements. The nasal septum is deviated to the right, as is the proximal extremity of the left nasal bone. The left anterior naris is larger than the right, with a resultant asymmetry of the apertura pyriformis.

Differences in the size and shape of the mandibular ascending rami are discernible, the left ramus being generally better developed, particularly as regards its coronoid and angular portions. Differences in the degree of development of the secondary markings due to the attachments of the internal pterygoid muscles suggest that the left muscle was functionally more vigorous than the right. The areas of attachment of the temporal muscles show no perceptible differences. There are no signs of injury anywhere to any of the cranial bones.

In this skull the cause can be referred to the loss of the right maxillary first permanent molar, which, by creating a tender area on that side of the mouth, led to a predominant functional activity of the masticatory musculature of the left side. It is an example of the wonderful plasticity of the bones during their growing period.

Section of Pathology

President—Professor WILSON SMITH, M.D., F.R.S.

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The Evolutionary Approach to Problems of Infection

PRESIDENT'S ADDRESS

By Professor WILSON SMITH, M.D., F.R.S.

FROM the outset the sciences of bacteriology and virology have been concerned very largely with the relief of human suffering and with the improvement of those animal and plant stocks required for man's needs and man's enjoyment. As a result there has been an undue emphasis upon bacteriological diagnosis based upon the precise characterization of the so-called ætiological agents of diseases. This in turn has led many medical men, including some pathologists and bacteriologists, to regard the host-parasite relationships of the various infective diseases as a series of associations between man, animal or plant host and one or other of a number of defined, stable, pathogenic micro-organisms. This is indeed the teaching, implied if not explicitly stated, of most textbooks of bacteriology; fortunately, students' textbooks of systematic virology have not yet appeared but probably they will follow suit in due course. Now, to anyone who makes a serious attempt to solve almost any problem of infection by the experimental method, such an outlook becomes wholly untenable. For routine diagnosis species definitions are, of course, essential, but the definitions are, at best, useful summaries of average behaviour and, at worst, descriptions of culture strains which have long passed into oblivion. I might describe in meticulous detail how I prepared concentrated staphylocoagulase ten years ago; I might even provide a descendant of the *Staphylococcus* strain which I used, but the chances that you could repeat exactly my experiences are extremely remote. Perhaps, the first lesson to be learnt by the research recruit in any biological science is that all living organisms possess amazing plasticity and constantly exhibit quite unpredictable behaviour.

This unpredictable behaviour is merely the outward and visible sign of evolutionary forces at work. Dissertations on the evolution of the bacteria and the viruses are most often concerned with the past and especially with origins. Speculations on these matters are full of interest but more important are the evolutionary changes which are going on now, ceaselessly and at remarkable speed, for it is these which are susceptible to experimental investigation and thus capable of providing clues for the solution of many fundamental problems. The tempo of evolutionary change in the bacteria and viruses must be kept clearly in mind if the potentialities of their effects upon infective processes are to be appreciated. If we accept as a reasonable estimate for many bacterial species a generation time of thirty minutes and for a man a period of twenty years, the whole span of man's evolution from his ape-like ancestors may be equated with an interval of about three months in the evolutionary history of the organism. Is it any wonder, then, that instability is such a striking characteristic of the bacteria and the viruses and can we any longer be surprised at the changing pattern of diseases, the multiplicity of strains of many species of infecting organism and the tangled skein of epidemiological phenomena?

My intention is to outline a few of the outstanding problems of infection in illustration of the type of problem which invites what may be termed the evolutionary approach, and to draw attention to some lines of work which, by adding to our knowledge of evolutionary processes, may eventually provide some of the answers.

OUTSTANDING PROBLEMS OF INFECTION

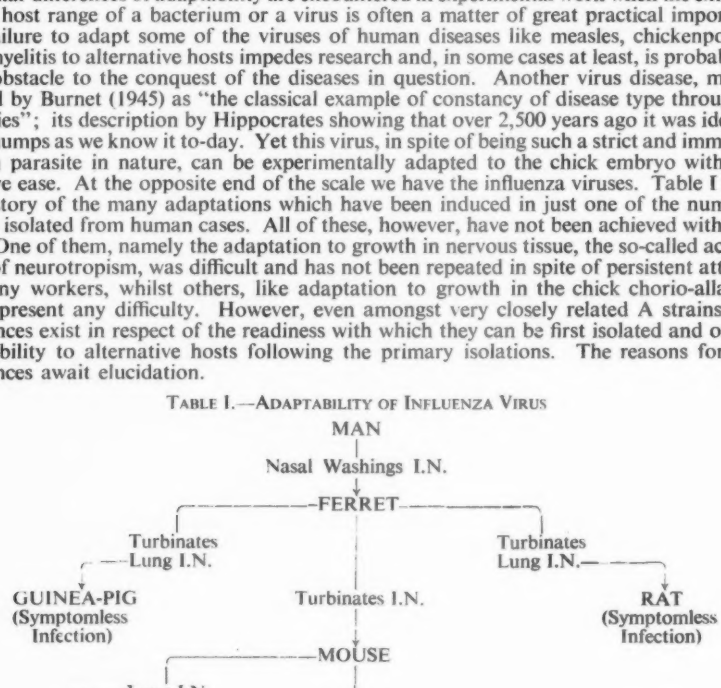
Variability of Specificity in Host-parasite Relationships.

One of the most interesting aspects of infection is the variability of specificity in the host-parasite relationships. A wide range of hosts or tissues susceptible to parasitization by a given micro-organism or by a phylogenetically related group of organisms connotes a history of past adaptations, the mechanism of which constitutes one of the great biological mysteries. Adaptability to environment is recognized as one of the chief characteristics of all living things, but the adaptations involved in specificities are dependent upon permanent and transmissible changes in the parasite and the tendency to exhibit such heritable changes varies enormously in different species. Thus tuberculosis is a natural disease of many animal species, whilst syphilis is a scourge for man alone. From a lifetime of study of the *Salmonella*, Bruce-White concluded that the scores of organisms comprising this genus must have had a common ancestry. This implies a remarkable series of adaptations from a single

progenitor; adaptation to strict human parasitism for the production of *S. typhi*, to rodent hosts for *S. typhi-murium* and *S. enteritidis*, to birds for *S. gallinarum*, to equines for *S. abortus-equi* and so on. On the other hand the *Neisseria*, as far as we know, are exclusively human parasites and, assuming a common progenitor for the meningococcus and the gonococcus, there has been no tendency through the centuries for adaptations to other host species. Similar contrasts are to be found amongst the viruses. Those of smallpox, alastrim and vaccinia show such close antigenic relationships that their common ancestry is unquestioned; indeed many workers would extend this phylogenetically related group to include all the pox viruses, whereas the agents of herpes of man, Newcastle disease of fowls, scrapie of sheep and many others appear to be incapable of enlarging host range either by the acquisition of new metabolic properties or by expansion into phylogenetically related groups.

Similar differences of adaptability are encountered in experimental work when the extension of the host range of a bacterium or a virus is often a matter of great practical importance. The failure to adapt some of the viruses of human diseases like measles, chickenpox and poliomyelitis to alternative hosts impedes research and, in some cases at least, is probably the chief obstacle to the conquest of the diseases in question. Another virus disease, mumps, is cited by Burnet (1945) as "the classical example of constancy of disease type through the centuries"; its description by Hippocrates showing that over 2,500 years ago it was identical with mumps as we know it to-day. Yet this virus, in spite of being such a strict and immutable human parasite in nature, can be experimentally adapted to the chick embryo with comparative ease. At the opposite end of the scale we have the influenza viruses. Table I shows the history of the many adaptations which have been induced in just one of the numerous strains isolated from human cases. All of these, however, have not been achieved with equal ease. One of them, namely the adaptation to growth in nervous tissue, the so-called acquirement of neurotropism, was difficult and has not been repeated in spite of persistent attempts by many workers, whilst others, like adaptation to growth in the chick chorio-allantois, rarely present any difficulty. However, even amongst very closely related A strains great differences exist in respect of the readiness with which they can be first isolated and of their adaptability to alternative hosts following the primary isolations. The reasons for such differences await elucidation.

TABLE I.—ADAPTABILITY OF INFLUENZA VIRUS



I.N. = Inoculation by the intranasal route.
I.C. = Inoculation by the intracerebral route.
C.A. = Inoculation by the chorio-allantoic route.
Am. = Inoculation by the amniotic route.

Possibly related to this kind of adaptability are the changes associated with attenuation and exaltation of virulence. In spite of whole symposia devoted to the subject of virulence, we still lack even general agreement on its satisfactory definition. The classical method for exalting the virulence of pathogenic bacteria is rapid passage through the particular host species in question; attenuation, on the other hand, is often achieved by serial cultivation in artificial media, particularly media devoid of native animal protein. But some pathogens fail to respond to such treatments and with others quite inexplicable sudden alterations occur. It is certain that there is more to it than the natural selection of chance mutants or the enhancement of particular metabolic processes and rate of growth by a particularly

favourable environment. That such mechanisms do exist and that they do at times participate in virulence changes, there can be no doubt, but they are quite inadequate as an explanation of all the phenomena. Hirst (1947) showed that during adaptation of an egg-passage strain of influenza virus to mice, abundant growth of virus in the lungs might occur during a number of serial passages without any overt signs of infection or the production of any detectable pulmonary lesions. Then quite suddenly a change ensues so that further passages result in the production of fatal pneumonia. The same phenomenon was reported by Friedewald and Hook (1948) with a strain adapted to the hamster. For six passages virus grew freely without causing any harm but at the seventh pass there was lung consolidation and death. Thus the faculty of growing freely within pulmonary cells does not of itself confer virulence upon the virus. If natural selection of a chance mutant was the whole story, one would expect the reverse phenomenon to occur sometimes, namely the supplantation of a fully virulent strain in the mouse's lungs by a mutant devoid of virulence, but with even greater rate of growth. So far as I am aware no such happening has ever been encountered. If, however, environmental factors, in this particular case the host cell constituents, can determine the direction of parasitic evolution by participating in some way or other in the process of mutation, then the tendency for such one-way change in any particular environment becomes readily understandable.

Variability of Antigenic Stability of Micro-organisms.

The antigenic instability of some infective agents and the sharply contrasted stability of others are also phenomena of great interest awaiting explanation. Reference has already been made to what might be termed the infectivity stability of mumps virus and this appears to be associated with considerable antigenic stability. Yellow fever and measles are other cases in point and the techniques of immunization against these diseases are based upon the assumption, justified by long experience, that rapid antigenic variations are unlikely to complicate the issue. Compare this with the state of affairs found amongst the influenza viruses. The two major types A and B give practically no cross reactions in immunological tests although recent work in my laboratory indicates that they are almost certainly phylogenetically related. The A-prime type is obviously related to A though quite easily distinguishable. Both A and A-prime types, however, comprise a large number of strains exhibiting antigenic differences which, though of a minor character, may be sufficient to account for some of the irregularities of epidemiological behaviour and some of the difficulties of conferring protection by means of vaccination. So labile is influenza A virus in this respect that it is doubtful whether any two strains, isolated from different outbreaks, are completely identical and even from the same outbreak distinguishable viruses may be obtained. Among the bacteria the gonococcus exhibits something of the same sort of antigenic lability. I often think, however, that antigenic variation has received undue attention because it is the sort of variation which lends itself most readily to laboratory investigation. Indeed all the adaptations and variations we have considered so far may be regarded as manifestations of the plasticity of micro-organisms. They are, of course, very far from being the only manifestations of plasticity. Table II shows the range of variations which have been recorded in the case of influenza virus A, admittedly one of the most variable viruses known. In a recent lecture Andrewes (1950*a*) asked "Where are the viruses allied to the older WS and PR8 strains which caused our troubles between 1933 and 1946? Have their fuses all fizzled out?" I suggest that not only their fuses, but they themselves have fizzled out, just as current strains will fizzle out in a short time to be replaced by their evolutionary descendants and that this must be so with such plastic labile forms. The real problem is to find by what mechanisms an A-prime strain of 1949 developed from a typical A strain of 1933.

TABLE II.—VARIABLE CHARACTERS OF INFLUENZA VIRUS

Antigenic Constitution Infectivity →	Host Range Adaptability to Lab. animals Tissue Specificity Clinical Effects
Immunizing Potency Toxicity Enzymic Activity →	Elution Rate Receptor Gradient
Interfering Potency Hæmagglutinin Stability → Hæmagglutination Activity	Fowl/Guinea-pig Ratio Serum Inhibition

Quite a number of specific questions arise out of these manifestations of plasticity. What is it which confers stability upon mumps virus and instability on influenza virus? Is it complexity of genetic substance, chemical composition of the virus proteins or texture of molecular structure? Does influenza virus contain chemical groups which are particularly reactive with other chemical substances found in various host environments? From what sort of precursor and at what stage of its evolution did mumps virus make its final jump to the present stable form? Why, with such ready experimental adaptability, does influenza

remain a disease restricted to human beings? Is it possible that the virus does in fact adapt constantly to lower animals, but in so doing suffers changes which make it irrecoverable in its original detectable form, and may not some such adaptation to occult form provide the mechanism for inter-epidemic survival of the virus? One is perhaps emboldened to present such a speculation from having in mind the truly fantastic behaviour of swine influenza virus in the pig, the swine lung worm and the earthworm as elucidated by Shope (1941, 1943).

Rickettsiæ-Proteus Relationships.

For those with a taste for armchair theorizing adequate scope for its indulgence is offered by the relationship between *Rickettsiæ* and *Proteus*. Routine laboratory diagnosis of several rickettsial diseases still rests upon the Weil-Felix reaction and Table III indicates the extent of the association based upon the sharing of common antigens. Now there are many examples of the sharing of common antigens by otherwise unrelated organisms, but to quote Topley and Wilson (1936): "So long as only one antigenic type of *Proteus* X was known, para-agglutination afforded a satisfactory enough explanation, but now that we know of at least two antigenic types of *Proteus* X, namely, OX 19 and OX K corresponding to two different types of *Rickettsia*, such an explanation is hardly tenable. If, that is to say, we regard *Rickettsia* and *Proteus* X as two entirely distinct groups of organisms, it is putting a strain on the imagination to expect that an antigenic variation in one organism should be accompanied by a corresponding antigenic variation in the other." In fairness I must add that this statement is not retained in the third edition of the book.

TABLE III.—RICKETTSIÆ-PROTEUS RELATIONSHIPS

Rickettsiæ	OX 19	OX 2	OX K
Epidemic typhus	+++	+	–
Murine typhus	+++	+	–
Brill's disease	+++	+	–
Rocky Mountain spotted fever ..	+	+	–
Boutonneuse fever	+	+	–
S. African tick bite fever ..	+	+	+
N. Queensland tick typhus ..	?	+	–
Rickettsial pox	–	–	–
Q. fever	–	–	–
Scrub typhus	–	–	+++

N.B.—In the Rocky Mountain spotted fever group of *Rickettsiæ* degrees of cross reactions with *Proteus* OX 19 and *Proteus* OX 2 may show considerable variations.

Felix himself subscribes to the view that *Rickettsiæ* and *Proteus* are genetically related, one representing a variant of the other. Others have suggested the acquisition of new antigenic factors by *Proteus* from its close association with *Rickettsiæ* within the bodies of typhus patients. There is a certain amount of experimental evidence in favour of this hypothesis and some of the new lines of investigation, which I shall refer to later, indicate that such transference of antigens or genetic factors, far from being unique to the *Rickettsiæ* and *Proteus* groups, may represent an evolutionary mechanism of very wide applicability.

Epidemiology of Influenza.

The epidemiological behaviour of influenza viruses brings into sharp focus a number of evolutionary problems. The origin of epidemics still remains a complete mystery in spite of the enormous amount of knowledge about the viruses themselves which has been garnered over the past two decades. One of the most puzzling features is the multicentric origin of outbreaks. Magrassi (1949) in his account of the Sardinian epidemic of 1948 reports the simultaneous appearance of the disease in ten centres with a case incidence of about 60%. He considers it impossible to account for the phenomenon by transportation of virus from centre to centre during the epidemic period and describes how shepherds isolated in open country came down at exactly the same time as the people living in communities. This, of course, is not an isolated instance—the same sort of thing has puzzled epidemiologists for years and has led many virologists to accept the theory that populations are seeded in inter-epidemic times with a virus which remains dormant until wakened into activity by some stimulus. Shope's work does indeed provide a little experimental evidence in favour of this theory, but the nature of the excitation factor in human influenza is completely unknown. Whatever it may be, it must be capable of inducing the same specific virus mutation simultaneously in the bodies of widely scattered individuals and to harmonize with such a concept the orthodox view of mutation as a purely random occurrence will obviously need drastic modification.

Much easier to accept is the concept of widespread infection with a dormant virus which only occasionally here and there, owing to chance stimuli, individual idiosyncrasy, secondary infections and so on, becomes activated to produce cases of disease of a sporadic nature. Indeed we know that this can and does occur as, for instance, in the case of the virus of herpes. But in this case the evidence indicates that the virus always begins its association with the human host as an overt pathogen. Are there instances of virus-host association which begin and often remain as purely harmless symbiotic relationships? Such a question at once calls to mind the Bittner Milk-factor which some virologists accept unequivocally as a virus, and which, in any case, constitutes one of the most cogent arguments in favour of what, for convenience, may be termed the virus theory of cancer. The reconciliation between the demonstrable virus ætiology of some neoplasms, like the fowl sarcomata and rabbit papillomatosis, and the complete failure to extract any similar infectious agents from most of the mammalian neoplasms is one of the outstanding problems of infection. Apart from the failure to transmit cancer by means of cell-free material, the histological diversity of the neoplasms presents perhaps the major objection to the virus theory, for the idea of a large number of different cancer viruses, all very widely seeded through the population and all remaining dormant in the majority of individuals puts too great a strain upon the imagination. Andrewes (1950*b*) suggests that the postulation of such a large number of cancer viruses is unnecessary as the same effects could be produced by a single basic prototype virus capable of mutating to produce different type tumours in different tissue environments. To my mind, in view of the frequency of some types of cancer, this puts an equally great strain on the imagination unless one accepts the possibility of environmental factors, not merely favouring a chance mutant, but controlling in some way the actual direction of mutation.

The theory that a somatic cell mutation provides the continuing cause of cancer is regarded by Andrewes as "the main visible alternative to the virus theory" (1950*b*). It is perhaps presumptuous of one who has never worked in the field of cancer research to express any opinion on such matters, but it seems to me that the two theories are not necessarily alternatives, but can be fused into a single hypothesis which, though admittedly a pure speculation, has at least the merit of resolving some of the difficulties inherent in either alone.

The Origin of the Viruses.

In his stimulating book "Virus as Organism" Burnet (1945) puts forward three possibilities: that the viruses arose as pathologically active fragments of animal or plant cells; that they are surviving descendants of primitive precellular forms of life; that they are the degenerate descendants of the larger pathogenic micro-organisms. Burnet strongly favours the last of these, but to me this hypothesis has always seemed both an over-simplification and intellectually repugnant by running counter to what appears to be the general trend of evolutionary development, namely the ceaseless trend towards increased organization. I am quite prepared to believe in retrograde evolution for isolated cases and I have no difficulty in accepting the origin of a complex virus like vaccinia by such a mechanism, but I suggest that it is stretching the theory of evolution by progressive enzyme loss rather far if we use it to explain the origin of plant viruses consisting of crystallizable nucleo-proteins. In rejecting categorically a fourth possibility, namely heterogenesis, Burnet says: "We can state dogmatically that there is no evidence whatever that any virus, whether its host be animal, plant or bacterium, arises *de novo*. Every virus particle like any other organism derives by genetic descent from some similar particle." With the first of these sentences one must perforce agree—there is certainly no positive evidence of the occurrence of heterogenesis—but with the second one may take issue. The trouble is that, like the continuous creation of matter recently postulated by Hoyle (1950), the creation of living from non-living material can never be detected in action. Possibly the most fundamental of all the attributes of living entities is their power of self-replication, so that once the decisive step of transformation from lifeless molecule to self-replicating molecule has been made, the latter will inevitably display biogenetical reproduction whenever and wherever it is detected.

Evolutionary Mechanisms of Micro-organisms

Each of these problems stems from our ignorance of the evolutionary mechanism of micro-organisms. The orthodox view that the sole determinant factor in evolutionary development is natural selection working upon mutants produced entirely at random fails to provide an adequate basis for ratiocination. The mere definition of some of the problems suggests the existence of alternative mechanisms in which environmental factors play a part in the acquisition, conservation and modification of heritable characteristics. It is easy to understand how injuries to the germ plasm by physical agents such as X-rays or nitrogen mustard might produce mutations by loss without any participation of environmental factors, but how are the mutations by gain achieved which are required in order to increase the range of the organism's activities as it evolves to higher grades of complexity? Relevant knowledge is very scanty, but the results of much recent experimental work are extremely suggestive.

Until very recent times the apparent absence of any sexual conjugation in the bacteria and viruses led to the almost universal acceptance of the tenet that reproduction in these micro-organismal forms occurred exclusively by binary fission. When I first took up the study of bacteriology any suggestion that bacteria might possess preformed elements analogous to mammalian chromosomes and mammalian genes was frowned upon as dangerous heresy. The few cases in which bacterial nuclei had been demonstrated were passed over as relatively insignificant exceptions. During the last few years, however, such structures have been unequivocally demonstrated in many species, including some of the common human pathogens. In this country Robinow (1942, 1944) has introduced new cytological techniques for the differential staining of chromatinic material in both sporing and non-sporing bacteria and found that different species possess their own characteristic arrangement of such material. Furthermore, the chromatinic bodies are shared out equally between the daughter cells during the process of cell division and are conserved through the resting phase of sporulation. Numerous workers in other countries have obtained similar results which, when taken together, provide complete refutation of the chief criticism that such appearances are due to artefacts. Mudd and Smith (1950), for example, in U.S.A. have demonstrated in *E. coli* by means of both electron and light microscopy, vesicular nuclei of characteristic shape, containing chromatin and of lower density than the enveloping cytoplasm. With regard to the viruses, all contain nucleo-protein and many of them reveal a chemical composition which relates them more closely to the nuclear protoplasm than to the cytoplasm of the cells of higher forms of life.

There is thus little doubt that the bacteria and viruses possess the kind of material used for the transmission of hereditary characteristics by sexually conjugating organisms. Is there any evidence that they possess also a mechanism for the interchange of such material between individuals of different clones which would substitute to some extent for sexual conjugation?

Type Transformation.

It is now over twenty years since Griffith (1928) first reported the transformation of pneumococcal types and passage of time has but served to emphasize the fundamental importance of his work. The transforming principle is a desoxyribosenucleic acid—one should speak rather of transforming principles for several have now been isolated from different pneumococcal types which, although quite indistinguishable by the available methods of chemical analysis, nevertheless exhibit high degrees of specificity of biological activity. The supreme importance of this work lies in the fact that it affords clear proof that living cells may take up from their environment preformed genetical material and incorporate it in the gene substance so that henceforth it is replicated as an integral component, indeed as one of the most important components, of the organism. Any agent which depolymerizes the nucleic acid destroys the biological activity of the transforming principle so that one wonders whether depolymerization and repolymerization of genetic material occurring in nature may not occasionally be the cause of spontaneous variations and adaptations. Pneumococci do not provide the only case of transformations of this nature; there have been several claims of analogous phenomena in respect of other bacterial species and the remarkable conversion of rabbit fibroma virus into myxoma virus by Berry and Dedrick (1936) was achieved by a similar technique and is probably based upon a similar mechanism.

Of course, such transformation by means of preformed genetic substance is a far cry from purposive modification of genetic processes by chemical means. As Ephrussi-Taylor (1950) puts it: "One should not conclude that we have finally acquired control over the biological properties of a genetic substance, for we have not yet influenced the properties of the gene-like transforming agents themselves nor have we created a genetic element *de novo*." In the last analysis, however, all mutations and variations of activity depend upon differences in chemical structure and I believe that we are now on the threshold of achieving such purposive control. The relation between chemical structure and mutation was beautifully demonstrated by Stanley (1943) in his studies on the multiple strains of tobacco mosaic virus. Each of these viruses is apparently a pure nucleo-protein; each gives distinctive symptoms in the leaves of Turkish tobacco plants; each represents a mutation from a progenitor virus. The nucleo-proteins of the various strains have the same general properties but exhibit differences in respect of the relative percentages of certain amino acids. One of them, Ribgrass virus, contains an amino acid, histidine, which is absent both from the parent strain and from all the other variants. It is difficult to see how enzyme systems involved in the synthesis of an entirely new amino acid can have been acquired without incorporation of new genetic factors. Stanley and his co-workers have attempted the *in vitro* mutation of tobacco mosaic virus by chemical means and although failing to induce heritable changes have succeeded in modifying virus activity by means of known and reproducible changes in chemical structure. Stanley himself appears to have no hesitation in attributing a determinant role to environmental factors. He says: "Unusual environmental factors such as might be provided within the cells of an unnatural host, or factors yet unknown, may affect the process of virus reproduction so that, instead of the

continuous production of exact replicas, there are produced occasionally similar yet slightly different active molecules."

Bacterial and Viral Recombination.

Let us now consider the evidence for the existence of mechanisms, other than sexual conjugation, which may provide a means for interchange of genetic factors. Employing the basic techniques and ideas evolved by Beadle, Tatum and others for the study of induced mutation and recombination of genetic elements in the heterothallic fungus, *Neurospora crassa*, several workers have adduced evidence of similar recombination in bacterial cultures of mixed clones. Investigations of such a nature are up against the difficulty of distinguishing between recombinants and mutants arising spontaneously, but favoured by the given environmental conditions. One must admit that some of the claims put forward are not beyond criticism in this respect. Recent work by Lederberg (1950), however, appears to leave no alternative to the recombinant hypothesis. He derived from a strain of *E. coli* two sub-strains which showed a wide variety of genetic differences. These are summarized as the relevant characteristics of the two parent strains A and B in Table IV. In respect of their resistance to two antibiotics and to a phage T5, and the nutritional requirements and sugar fermentations listed, A and B are exactly complementary. It is important to realize that each characteristic is determined by a separate gene and furthermore that it is extremely rare for spontaneous mutation to affect more than one gene at a time. Thus a derivative of A possessing only one character changed to the B type or *vice versa* may be due either to a spontaneous mutation or to genetic interchange, but a derivative strain exhibiting multiple characteristics of each parent type is almost certainly the result of genetic recombination. The fact that the parent strains had complementary drug resistance to the two antibiotics, streptomycin and sodium azide, facilitated the isolation of recombinant organisms. After growing the parents together for some hours in ordinary nutrient broth the mixed cultures were explanted in streptomycin-azide agar so that growth of all the organisms which had remained true to parent type was inhibited. Lederberg reports the characteristics of 98 clones obtained in this way, but in Table IV I have shown only those offering the most convincing evidence for recombination. Seven clones were indistinguishable from either one or other parent except for their double drug resistance and these may legitimately be accepted as mutants. The remainder showed mixed A and B characters indicative of genetic recombination. This does not, of course, reflect the proportional tendency to mutation *vis-à-vis* recombination, for all mutants other than those acquiring double drug resistance would fail to grow in the explant medium.

TABLE IV.—BACTERIAL RECOMBINATION (AFTER LEDERBERG)

Strain of *E. Coli*	Streptomycin	Azide	Phage T5	Growth factor requirements: Threamine	Leucine	Thiamine	Methionine	Sugar fermentations: Lactose	Maltose	Xylose	Mannitol
Parent A	+	−	+	+	+	+	−	−	−	−	−
Parent B	−	+	−	−	−	−	+	+	+	+	+
A. Mutant	+	+	+	+	+	+	−	−	−	−	−
B. Mutant ..	+	+	−	−	−	−	+	+	+	+	+
Recombinant α ..	+	+	−	−	+	−	−	+	−	+	−
Recombinant β ..	+	+	+	−	−	+	−	−	−	+	−
Recombinant γ ..	+	+	+	−	−	−	−	−	−	+	+

It is noteworthy that very poor yields of recombinants were obtained if the parent cultures were simply mixed together immediately before plating out; as one would expect, the mechanism of genetic interchange is probably only operative during the growth cycle of the organisms. How the exchange is effected, whether by fusion of two or more cells with subsequent division or by a disintegration of cells into subcellular units with subsequent recombination, we do not know. It is probable that the mechanism of different species follows different patterns, for in some species fusion of two cells analogous to the sexual conjugation in heterothallic fungi has been reported, in others the formation of a syncytium, in *Phytomonas tumefaciens* the fusion of the chromatinic contents of many individual bacilli joined together at their tips and so on. The crucial fact is that such genetic interchange provides bacteria with the means of acquiring new genetic elements. Nor is it impossible that the new elements may be acquired elsewhere than from other bacteria of the same species. The cytological observations of Luria and Human (1950) on *E. coli* infected with T phages revealed a disruption of the chromatinic bodies of the bacilli followed by swelling of the cells and their filling up with granular chromatin. These authors suggest that with phage infection the bacterial genes are replaced by phage genes as the directive agents for further protein synthesis.

In those bacteria which are destined to undergo death by lysis production of bacterial protein may be entirely replaced by production of phage protein but in the wide range of phenomena involved in bacterium-phage associations, including constant phage mutations and the induction of bacterial lysogenicity, it seems to me that there is some justification for the belief that exchanges of genetic material between the two classes of organism may occur. Lysogenicity indeed offers one indisputable example of mutation conditioned by the interaction of a micro-organism with its environment.

Amongst the phages themselves recombination has also been shown to occur. The simultaneous growth of two related phages in the same bacterial cell may result in the production of a new phage having characters acquired from each of the two progenitors. The simplest explanation is that there has been an exchange of genes. In the phage T2 a different mechanism has been demonstrated, namely a separation of the gene structure and its recombination into a new pattern resulting in changed properties of the organism.

The only published work on recombination of animal viruses of which I am aware, is that of Burnet and Lind (1949) with strains of influenza A virus. Burnet gave an account of these investigations during his recent visit to this country, and I would like to outline the salient points. The isolation of a neurotropic strain of influenza virus by intracerebral passage through animals has been achieved once only by Stuart-Harris in spite of numerous attempts by other workers. This indicates that the mutation involved is a rare mutation unlikely to occur by chance except very occasionally. The neurotropic strain kills mice uniformly at about a week's interval after its inoculation into the brain whereas all other strains are innocuous when so inoculated. Burnet and Lind studied the interference effects between this strain and others which are clearly differentiated by their antigenic structure and certain other characteristics such as hæmagglutinin thermolability. From mice inoculated with virus mixtures in which symptoms of encephalitis were delayed by the interference effect, strains were recovered frequently which possessed neurotropism together with other characteristics peculiar to the non-neurotropic virus. In this case it is even more difficult than in the case of bacterial recombinant experiments to exclude the possibility of derivative strains being mixtures, but Burnet is quite convinced that this is not the explanation of his findings. Passage through batches of eggs at limiting dilutions provides an *in vivo* technique analogous to the plating out of bacterial cultures for the isolation of single colonies. With mixed virus strains this would be expected to lead to the recovery of one type from some of the eggs of a batch and the second type from other eggs. Burnet and Lind, however, found that with their recombinant strains all the positive egg fluids of a batch showed the same assortment of marker characters. Moreover each of the recombinants obtained shows at least one character not shown by either parent. It is suggested that during the early phase of cell infection a breakdown of the viruses into sub-units occurs followed by their recombination in different patterns to give once more fully formed, infective, elementary bodies. There is indeed a considerable weight of evidence to support the view that such breakdown and re-aggregation forms part of the normal growth cycle of influenza virus. Hoyle (1948) claims that virus inoculated into the allantoic cavity of the chick embryo is taken up by the cells lining the cavity to be converted into a non-infective and non-hæmagglutinating form which multiplies before being reconverted into the normal infective and hæmagglutinating virus. He found that large amounts of so-called soluble antigen are produced before the egg-fluids become infective and thinks that this antigenic material may represent the pre-infective phase of the virus. Similarly the Henles (1949) demonstrated a regular sequence in the development of various types of virus activity within inoculated eggs—first a rise of complement-fixing activity, then a rise of hæmagglutinating activity and subsequently a rise of infectivity titre. It is extremely significant that degradation of virus by ultraviolet light follows the sequence in reverse order.

Cytoplasmic Primers.

Although pertaining to an entirely different class of organism, namely *Paramœcium aurelia*, recent work on the so-called plasma genes or cytoplasmic primers is germane here because it has brought to light convincing evidence that heritable characters may be determined by the interaction of nuclear genes and cytoplasmic substances. Some strains of paramœcium, known as killer strains, render the nutrient fluid in which they are grown lethal for non-killer strains. The characters, killer and non-killer, are thus alternate characters and it has been shown that they depend upon a pair of allelic genes K and k, together with a cytoplasmic factor kappa, K being dominant for killer character. The various possibilities of genetic combination are shown in Table V.

Sonneborn (1945) has been able by appropriate techniques to obtain each variant for study. In mating there is usually an exchange of nuclei but no cytoplasmic interchange, but under certain conditions cytoplasmic interchange does occur so that kappa may be introduced into organisms with the genetic combination kk. Such strains, with the two recessive genes plus kappa, act as killer strains for a few fission generations until all detectable kappa is lost whereupon they revert to ordinary non-killers. Introduction of kappa into organisms

TABLE V.—INTERACTION OF NUCLEAR GENE AND CYTOPLASMIC PRIMER IN *Paramœcium aurelia*

Allelic genes = K (dominant) and k (recessive) } Determining alternate characters, Killer and Non-killer
Cytoplasmic Primer = kappa }

Killer strains	Non-killer strains
KK + kappa	KK
Kk + kappa	Kk
	kk
	kk + kappa

with either two dominant genes or one dominant and one recessive on the other hand converts these into permanent killer strains. Thus it appears that kappa alone determines the killer character as such, but that K is essential for its synthesis. Most significant of all is the fact that the dominant gene K can *not* initiate the synthesis of kappa; some kappa must be present in the cytoplasm before K can fulfil its function of synthesizing more of it. Hence the name cytoplasmic primer, from analogy with the necessity of priming certain types of pump at the start of pumping operations. The similarity of kappa behaviour with that of many viruses is striking. The hypothesis accepted by Sonneborn and supported by further direct experimental evidence—which must be passed over for lack of time—is as follows. The macro-nuclear gene K can combine with kappa drawing it into the nucleus from the cytoplasm. If sufficient kappa is present some remains in the cytoplasm, conferring killer character, but kappa combined in the nucleus is inactive. Normally kappa is released into the cytoplasm of a killer strain from the macro-nucleus when it disintegrates into micro-nuclei at the time of fertilization. The implications are that kappa, when combined with K, becomes an integral part of the gene, the role of K being to reproduce both itself and whatever is combined with it.

THE POSSIBILITY OF GENETIC INTERCHANGE BETWEEN HOST AND PARASITE

I have been able in the time available merely to sketch in bare outline just a few of the many experimental investigations which are rapidly extending our knowledge of the mechanisms involved in the hereditary transmission of characters. These few alone, however, provide fairly conclusive indications that environmental factors may participate directly in such mechanisms, that gene interchanges may occur between bacterial cells or between virus elementary bodies, that dissimilar organisms such as bacteria and their phages may share in a genetic shuffling and that cytoplasmic constituents in combination with nuclear elements may play an essential role in hereditary transmission, in addition to fulfilling their functions as separate entities. All these mechanisms are of obvious significance in the type of infection problem which I illustrated earlier. For example, it is much easier to explain the sudden production of a pandemic influenza virus, with its extraordinary communicability, increased growth rate, increased toxicity, increased invasiveness and peculiar antigenic constitution by the process of genetic interchange between two or more progenitor strains than by a single-step chance mutation or even a sequence of such chance mutations. Again the general trend of evolutionary development towards higher organization is not difficult to understand on the basis of the recombinant hypothesis. There remain, however, certain phenomena of infection for which the various hypothetical mechanisms so far mentioned appear to be inadequate. With great trepidation, and merely as an armchair speculation quite devoid of factual supporting evidence, I suggest that genetic exchange or genetic combination may occur between some micro-organisms, especially the viruses, and the cells of their animal hosts, including man. At first thought, all our knowledge concerning the strict species specificity of sexual reproduction, the non-antigenicity of homologous tissue proteins contrasted with the profound effects of the inoculation of heterologous protein, the incompatibility of dissimilar blood cells and so forth appears to militate against the possibility of any such genetic intercombination. One must remember, however, that fundamental similarities as well as differences exist in widely separated species and genera. Some of the basic mechanisms of metabolism are similar or even identical in widely divergent forms of life. All living organisms require the same score or so of amino acids and employ closely similar enzymes and chains of enzyme reactions for their synthesis. For example the Ornithine cycle in *Neurospora* is very similar to the cycle in the mammalian liver postulated by Krebs and Henseleit (1932).

Furthermore, the many similarities between certain viruses and genes, each consisting of nucleo-protein, have led to the postulate that the viruses may in fact be aberrant genes which have released themselves from the controlling forces which normally retain them within the chromosomal organization. Be that as it may, the intimate association of the genetic substance of virus and host cell in the various phases of cell parasitization must provide unique opportunities for genetic shuffling. Whilst the virus is passing through the cycle of its reproduction, the cell is being subjected to the disruptive forces of infection. The genes of both are known to be susceptible to the same type of injurious agents and to

respond to some of them by an increased mutation rate. A mutation often consists simply of a rearrangement of atoms in the molecule and as Schrödinger (1948) has said: "It would be absurd to exclude the possibility of any exchange with the environment."

How far would a mechanism of genetic interchange between host cell and parasite —could it be shown to occur—help to elucidate unsolved problems of infection? The possibilities thus opened up are almost endless. A few of the problems which may be profitably reconsidered along these lines are:

(1) The origin of new viruses.
(2) The contrast between the extreme lability of some viruses and the stability of others.
(3) The relationship of influenza mutants to epidemiological phenomena.
(4) The variability of infective agents in respect of their adaptability to new hosts and new tissues.
(5) Exaltation and attenuation of virulence.
(6) The antigenic constituents of influenza viruses which appear to derive from the hosts in which they are propagated.
(7) The genesis of neoplasms.

About this last I would like to add a little. It has been said that the difficulty about discovering the cause of cancer is that we know too much about the causes of cancer. It is a paradox with much underlying truth. The urgent need is for the revelation of a synthesizing factor which would relate the several different causes into a comprehensive ætiological mechanism. Cell-virus genetic inter-combination, along lines somewhat similar to the K-kappa association in *Paramœcium*, giving rise to a cell mutant with the character of unrestrained cell growth, would go far towards providing such a synthesis. It would weld together the virus theory and the cell mutation theory considered by Andrewes to be the only reasonable alternatives; it would resolve the chief difficulty of the present virus hypothesis presented by the histological diversity of neoplasms; it would provide a reasonable role for the many carcinogenic agents of diverse physical and chemical nature and it would account for the variable behaviour of neoplasms in respect of virus filtrability.

My usual advice to the young research worker who comes to me with some attractive hypothesis is to devise an experiment which will put it to the test. Some at least of the speculations which I have put forward possess the merit that they are open to the experimental approach. Thus it would be worth while attempting the production of a new *Proteus* strain, related say to *Rickettsia burneti* by manipulating both agents together in the chick embryo and attempting to isolate *Proteus* mutants by agglutination with anti-rickettsial serum. Or a new strain of influenza virus capable of epidemic spread in ferret colonies might evolve in animals infected with multiple strains. My hope is that something I have said here may lead some young worker to undertake investigations of such nature and it will matter not one jot if the results of his experiments demolish completely the hypothetical structures from which they took origin.

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Section of Orthopædics

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[*April* 4, 1950]

President—Norman Capener, F.R.C.S.

Henry Hugh Clutton (1850–1909)

A Centennial Note

By W. R. Bett

Some surgeons have successfully immortalized themselves through a new disease-entity, a cunning operation, or a neat instrument to which they—or adoring disciples—have in perpetuity attached their name. To the majority of medical students to-day Henry Hugh Clutton, who was born a century ago, on July 12, 1850, is imprisoned in the eponymic mausoleum of *Clutton's Joints*. In the words of Sir Thomas Browne, " to keep men out of their Urnes, and discourse of humane fragments in them, is not impertinent unto our profession".

What are now universally known as "Clutton's Joints" were first described by Clutton, then Assistant Surgeon to St. Thomas's Hospital, in a paper entitled "Symmetrical Synovitis of the Knee in Hereditary Syphilis", in the *Lancet*, 1886 (i), 391–3. This is one of the classic contributions to medical literature, distinguished by its brevity, lucidity, modesty, and completeness. The author describes 11 cases, including 7 of his own; their average age was 13, and they were all victims of hereditary syphilis. He stresses the symmetry of the affection, freedom from pain, the long duration of the symptoms, and the free mobility of the joints on passive movement throughout the course of the disease. He points out the similarity to interstitial keratitis, both conditions being exceedingly chronic, with little or no destructive changes in the tissues involved; both being liable to relapses and "not very amenable to treatment". He advocated antisyphilitic remedies, such as mercury and potassium iodide. Clutton's statement, "The disease is, I am sure, a rare one, so that only a few cases will come under the observation of any one surgeon", is still generally accepted, the incidence being less than 1% in congenital syphilis.

Henry Hugh Clutton (1850–1909)
(Reproduced by permission from *St. Thomas's Hospital Gazette*, 1909)

"I am at a loss to explain", Clutton continues his account, "why the knees should be affected in preference to other joints. It is probable that, with further observation, the knees will not be found to occupy this solitary distinction, and that other joints will be seen to be affected in a similar manner". In the sixty-four years that have passed since this statement was made cases have been reported in the literature in which the elbows, shoulders, wrists, fingers, and ankles were affected, but these are admittedly rare compared with involvement of the knees.

Clutton's professional career was intimately associated with St. Thomas's Hospital, which he entered as a student in 1872. Four years later he became a Fellow of the Royal College of Surgeons of England, was elected Assistant Surgeon with charge of the Department for Diseases of the Ear in 1878, and full Surgeon in 1891. He was Surgeon to the Victoria Hospital for Children in Tite Street, Chelsea, from 1887 to 1893. A careful observer, he kept records of all his important cases in his own handwriting and took great pains to follow up the histories of both private and hospital patients. A vivid, popular clinical teacher, who based surgery on pathology rather than on anatomy, on his rounds he hurried into the wards with a mixture of "a walk, a run, and a slide", leaving the crowd of students far behind. The bearded man with the twinkling eyes was often called the "Students' Friend". The last years of his life were marred by ill-health.

Polyostotic Dysostosis.—H. H. LANGSTON, F.R.C.S.

Miss D. B.

History.—At the age of 12 the patient noticed a swelling of the left side of the face. This slowly increased and enlargement of the left frontal region, zygoma and left jaw developed. In 1936 exploration for parathyroid tumour by Sir Gordon Gordon-Taylor, with negative result.

In December 1948 she was admitted to the Royal Hants County Hospital, complaining of breathlessness due to a left-sided pleural effusion.

On examination.—Marked deformity and enlargement of the whole of the left side of the face and jaw. Massive left pleural effusion. Some irregularity of the lower ribs of the left side.

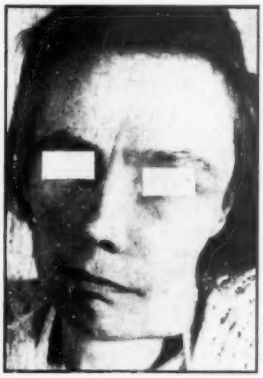

FIG. 1.—Illustrating involvement of skull, malar bone and mandible.

Effusion aspirated: Fluid contained no malignant cells; guinea-pig inoculation negative.

X-rays.—Polyostotic dysostosis involving left side of the skull, malar bone, jaw, the ribs on the left side, the left humerus, left fifth metacarpal and other phalanges of the left hand but no other bones (*see* Figs. 1–7). Pelvis and other limbs entirely normal.

No abnormality of blood picture apart from a consistently raised alkaline serum phosphatase ranging from 28 to 43 K.A. units in 3 estimations.

Section of tumour of jaw.—Macroscopic: Specimen consists of three fragments of extremely hard and compact bone-like material showing extreme congestion of the matrix. The outer surface is smooth and does not show any signs of erosion.

FIG. 2.—Skull, lateral.

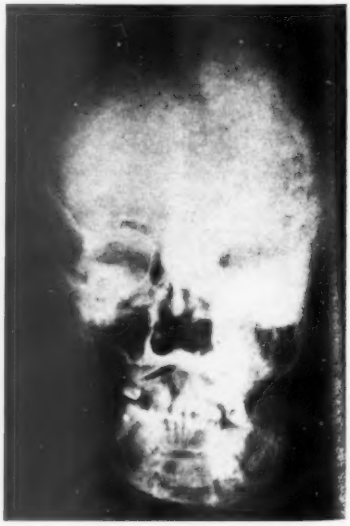

FIG. 3.—Skull, A.P.

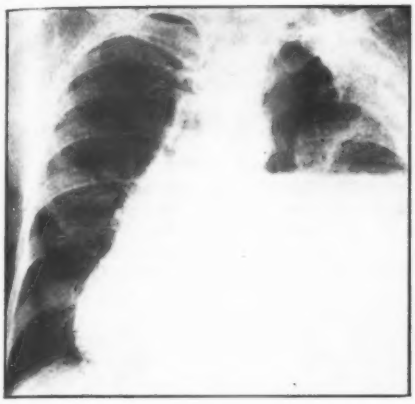

FIG. 4.—Illustrating pleural effusion and rib involvement on left side.

FIG. 5.—Left mandible.

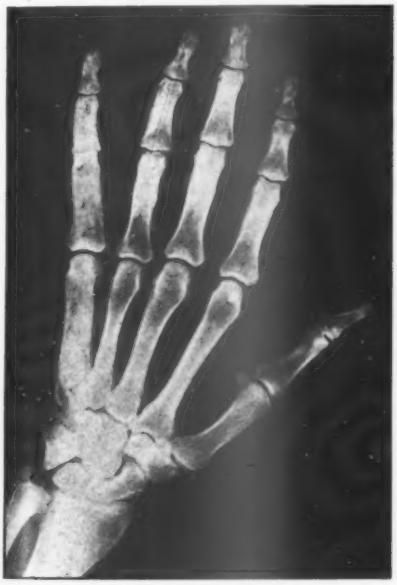

FIG. 6.—Left hand.

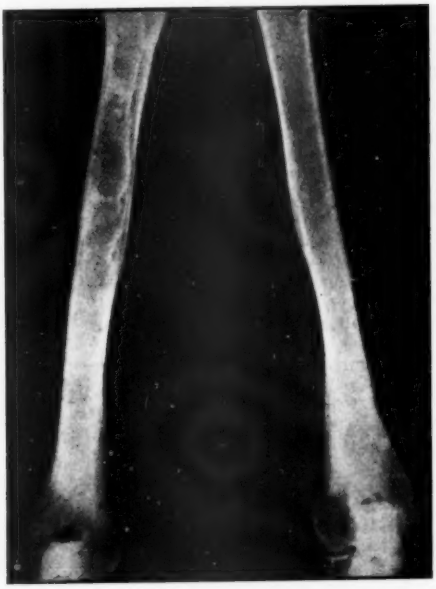

FIG. 7.—Humeri, illustrating cystic involvement of shaft of left humerus.

Microscopic: Irregular bony trabeculæ, of arrangement similar to compact bone, are accompanied by fibrosis in the spaces between them; this fibrosis is highly cellular, the cells being mostly of mature type. Blood vessels are not numerous but hæmorrhages are present in places; osteoclasts are not seen. This picture fits in fairly well with polyostotic fibrous dysplasia.

The case is considered of interest in view of the distribution of the bone changes and the acute development of a pleural effusion on the left side which is presumed to be related to the involvement of the ribs on the left side by the bone dystrophy.

The patient is shown with the kind agreement of Dr. Kenneth Robertson under whose care she was in the Royal Hants County Hospital, Winchester.

Subacute Aleukæmic Lymphatic Leukæmia Presenting as Compression Fracture of the Dorsal Spine.—R. H. METCALFE, M.D., F.R.C.S.

S. B., girl aged 7.

In September 1949 she fell off her cycle and a week later developed pain in the dorsal spine, which became severe.

November 1949: X-rayed. Reported to have crush fracture of dorsal vertebræ 6 and 8 with osteoporosis.

December 1949: Admitted to Joyce Green Hospital. Mantoux 1 : 100 positive. B.S.R. 63 mm. in one hour. A provisional diagnosis of tuberculosis of the spine was made.

January 13, 1950 (Fig. 1).—Transferred to Queen Mary's Hospital for Children, Carshalton. Local tenderness and kyphosis at lower dorsal level. Reflexes of both arms and legs exaggerated. Gross muscle spasm. Immobilization on spinal carriage at once relieved pain.

February 19, 1950 (Fig. 2): Child very pale and obviously ill. Ecchymoses right loin, left forearm and right cheek. Glands palpable in neck, axilla and groin. Œdema of both feet. Liver enlarged three fingerbreadths below costal margin.

Blood count: Hb 3·25 grammes %; R.B.C. 860,000; C.I. 1·26; W.B.C. 2,200 (polys. 5%, lymphos. 95%). Bone marrow smear: Almost all cells were lymphocytes, 20% being immature and some showed mitotic division.

The child died on February 22, 1950.

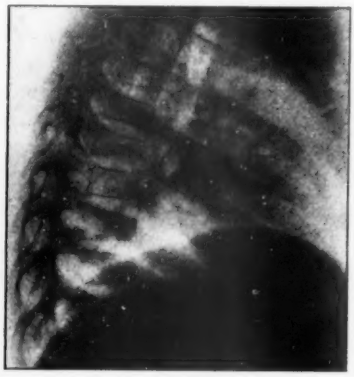

FIG. 1.

FIG. 2.

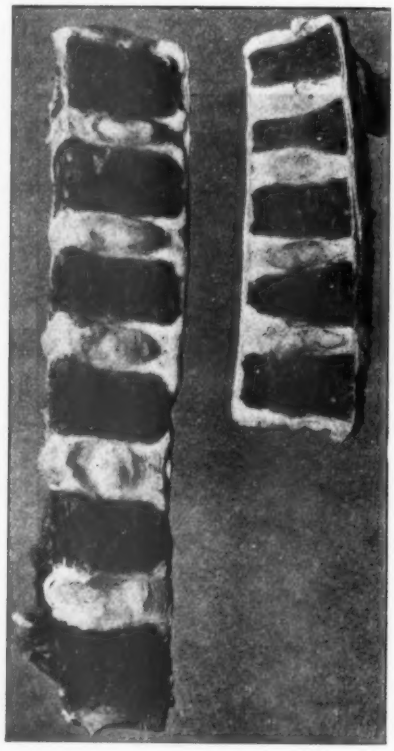

FIG. 3.

FIG. 1.—Lateral X-ray of spine, 13.1.50, shows compression D.V. 6 and 8.

FIG. 2.—Lateral X-ray of spine, 1.2.50, shows gross involvement L.V. 4.

FIG. 3.—Section of spine, 23.2.50. Specimen on right shows compression of dorsal vertebræ.

Mr. H. H. Langston said that he had had a similar case, presenting in the same way—a child with acute pain in the back, and, as far as could be recalled, no history of injury. There was dorsal kyphosis, with a great deal of pain and muscle spasm. On X-ray examination numerous dorsal

vertebræ were found to be compressed. The child did not survive very long, but long enough to enable a blood picture to be obtained and a diagnosis made.

Mr. **Metcalfe** added that his patient remained well until four days before she died.

Generalized Neurofibromatosis: Involvement of Right Tibia with Two-inch Lengthening and Forward Bowing.—R. H. METCALFE, M.D., F.R.C.S.

E. W., a woman aged 39.

History.—Patient has suffered from cutaneous neurofibromatosis and cafe-au-lait patches as long as she can remember (Fig. 1). Swelling and lengthening of the right lower leg was first noticed at the age of 4. The swelling has gradually become worse and in recent years very painful. The increased length has caused difficulty in walking. No family history of the condition. She has three normal children.

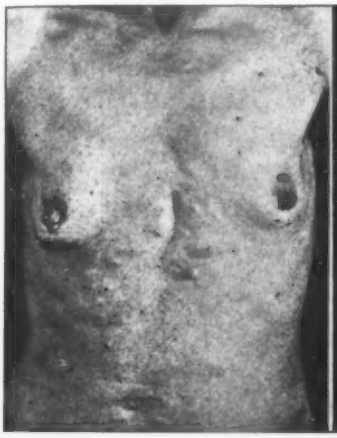

FIG. 1.—Showing cutaneous lesions on chest and upper abdominal wall (neurofibromatosis).

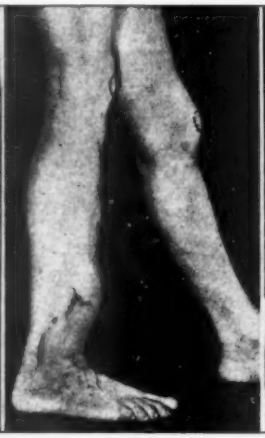

FIG. 2.—Condition of right leg before operation.

FIG. 3.—Condition after operation, leg shortened by excision of 2 in. of tibia, with satisfactory correction of the gross deformity.

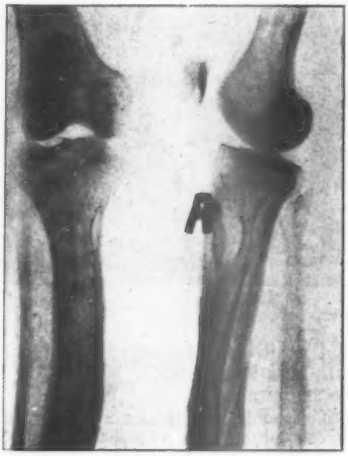

FIG. 4.—Radiograph taken 30.10.48, showing condition before operation.

FIGS. 5 and 6.—Radiographs taken 3.8.50 showing the fracture to be united.

On examination.—Two-inch lengthening and gross forward bowing of the right tibia, with eversion of the foot. Astragalus at 45 degrees (Fig. 2).

28.10.49: Osteotomy of tibia and fibula to shorten bone and correct forward bowing.

3.12.49: Discharged home in plaster.

3.5.50: Sound bony union. Walking without plaster (Figs. 3, 5 and 6).

Pathological Dislocation of Hip Following Osteomyelitis.—H. L-C. Wood, M.S.

J. D., boy aged $3\frac{1}{2}$ years.

26.1.47: Admitted to Belgrave Hospital with swelling of right thigh of six days' duration. Acute osteomyelitis upper end right femur diagnosed. Treated with sulphadiazine and penicillin 50,000 units six-hourly.

Operation same day by Mr. Selwyn Taylor: Subperiosteal abscess opened. Cortex of bone drilled. Put in plaster.

6.2.47: X-ray showed pathological dislocation right hip (Fig. 1). Traction applied.

14.3.47: Otitis media, right ear. Mastoiditis.

21.4.47: Discharged from hospital.

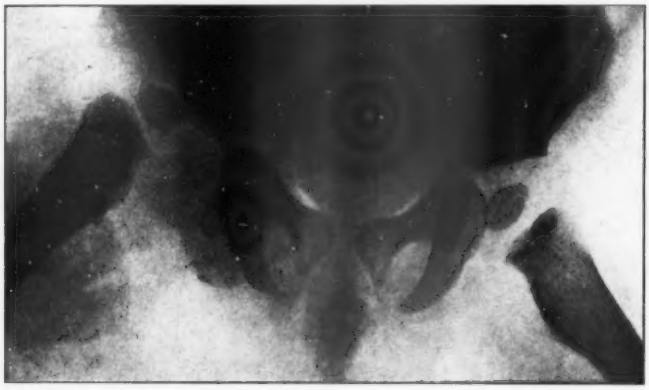

Fig. 1.

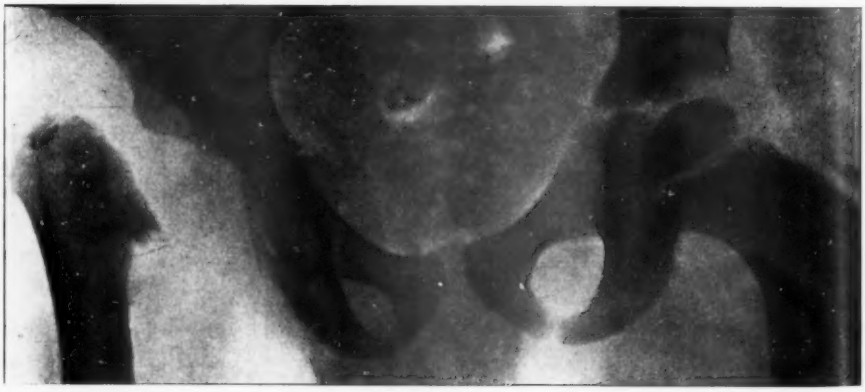

Fig. 2.

Present condition.—Walks well. Trendelenburg sign positive. Shortening one inch. X-ray shows absorption of head and neck of femur with false joint (Fig. 2).

Case shown for help in deciding further treatment to stabilize joint.

Mr. A. L. Eyre-Brook said that he thought an angled osteotomy should be done later on to improve stability of the joint. This was a very common problem. He did not know why that particular situation was so often picked on for osteomyelitis in infancy, but it was a common pattern.

Mr. H. L-C. Wood asked at what age an osteotomy should be done.

Mr. A. L. Eyre-Brook said that the age should be 10 or 12.

Non-Suppurative Osteomyelitis of Lumbar Vertebræ.—H. A. KIDD, F.R.C.S.Ed., M.R.C.O.G.

E. R., boy, aged 14.

History.—July 8, 1949, injury to spine when another boy knelt on him, with local pain and bruising. When seen at the Casualty Department, St. Helier Hospital, on July 14, there was local tenderness over the right lumbar transverse process 4 and 5 and some bruising. *X-ray*: No evidence of bony injury. Pain improved but recurred in September.

Past history.—Boils and otitis media 1946. Father treated at home with severe pulmonary tuberculosis.

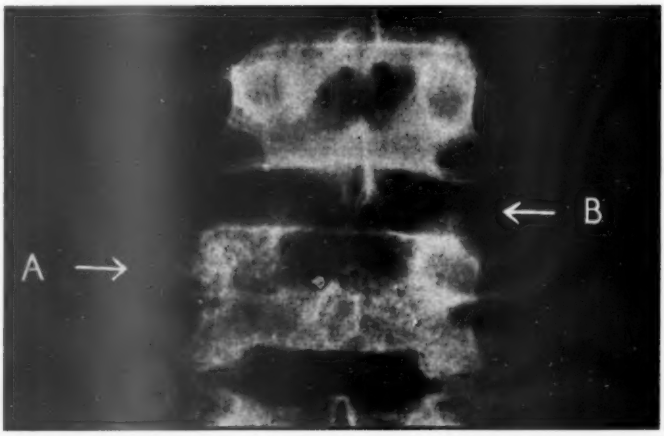

FIG. 1 (30.9.49).—A.—Expansion and rarefaction of fourth right transverse process and inferior pedicle of L.3. B.—? fracture. ? ununited epiphysis inferior pedicle left L.3.

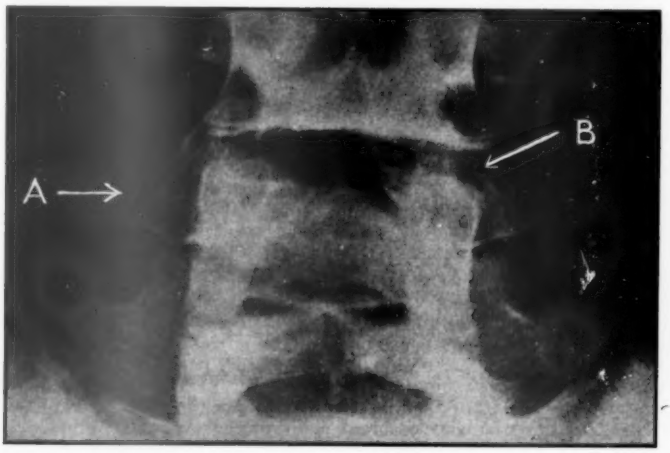

FIG. 2. (27.6.50).—A.—Complete resolution of inflammatory process. B.—Complete union of inferior pedicle of L.3.

Examination.—There was local tenderness over the right third lumbar transverse process, and in the erect posture, marked tilting of the pelvis, producing ½ in. shortening of the right leg. On flexion of the spine there was scoliosis to the right.

Investigations.—Mantoux test negative. B.S.R. (4.10.49) 47 mm./hr. Blood count: R.B.C. 4,730,000; Hb. 90%; W.B.C. 6,450 (polys. 57%, eosinos. 3%, lymphos. 37%, monos. 3%). Bence-Jones protein negative. During the twelve days before operation temperature twice rose to 99·4° F.

X-ray report showed: A.—Transverse process of fourth lumbar vertebra to be expanded and rarefied, pedicle also being involved. B.—? fracture line in the left inferior pedicle of the third lumbar vertebra, ? ununited epiphysis.

Sir Thomas Fairbank saw the case in consultation and thought it was probably a chondrosarcoma, and advised biopsy.

Operation (11.10.49).—Laminectomy with removal of third and fourth spines and right transverse process L.4. Gelatinous infiltration of the soft tissues around the transverse process, although the process itself consisted of spongy, friable and porous bone. This osteoporosis extended into the pedicle. Five pieces were taken for section. The cord was left decompressed and the wound closed.

Convalescence was uneventful except for some discharge from the wound on October 24, 1949. Organism was *Staph. aureus*, and responded to penicillin and sulphadiazine.

A plaster of Paris spinal jacket was applied and this was worn for three months.

Pathological report on sections.—(1) *Soft tissue overlying lamina*: Non-specific chronic inflammation. (2) *Pieces of transverse process*: Fibrosis and chronic inflammatory change in the marrow spaces with non-specific chronic inflammation, hæmorrhage, and necrosis in the soft parts. (3) Chronic granulation tissue. (4) Chronic granulation tissue in marrow spaces. (5) Granulation tissue with spicules of bone still acutely inflamed.

No evidence of neoplasia or tuberculosis seen in any of the material.

The patient was discharged to a convalescent home on November 13, 1949, in a plaster of Paris jacket.

X-rays (1.4.50) show regeneration of the lumbar transverse process and a nearly normal appearance of the vertebra. The ? fracture ? ununited epiphysis shows union to be nearly complete.

The plaster was removed in March. Movements of the spine were full and the small sinuses in the scar were healed. Fig. 2 shows the condition on 27.6.50.

Differential diagnosis.—(*a*) Sarcoma, osteoblastoma, tuberculosis, sclerosing osteitis and non-suppurative osteomyelitis. (*b*) Fracture of inferior pedicle or ununited epiphysis.

Sir William McKenzie, 1947, reported cases of sclerosing otitis media, but these occurred in the long bones and were similar to Garre's osteitis.

Jaffe and Lichtenstein, 1940, reported a number of osteoid osteomata, three of which occurred in the vertebræ. These, however, affected the bodies of the vertebræ, though they fell into the age-group 10 to 25 and were not associated with pyrexia.

Guri, 1946, reports 7 cases of subacute osteomyelitis of the spine, but these again occurred in the bodies of the vertebræ.

Comments.—This case was shown as one of non-suppurative osteomyelitis of the lumbar vertebræ. There was a history of injury with local bruising and negative X-ray, followed after a latent period of six weeks, by a recurrence of pain, slight pyrexia, B.S.R. 47 mm./hr. and negative Mantoux test. X-ray showed expansion and osteoporosis of the third transverse process and pedicle of the fourth lumbar vertebra. There is now no deformity of the spine and the spinal movements are full and painless.

REFERENCES

GURI, P. J. (1946) *J. Bone Jt. Surg.*, **28**, 29.
JAFFE, H. L., and LICHTENSTEIN, L. (1940) *J. Bone Jt. Surg.*, **22**, 645.
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Melorheostosis (Leri).—J. G. O'CONNELL, F.R.C.S.Ed.

Miss R. B., aged 18, first attended London Hospital on 3.9.49 complaining of pain in the right tibia which had been present for nine years. Pain described as intermittent, usually in the nature of a dull ache, present on exercise and also at rest in bed. At the age of 4 she had erysipelas in that leg; otherwise nothing relevant in her past history.

On examination.—Diffuse swelling of the right leg (Figs. 1 and 2). Some increased local heat. Tender on pressure over crest of the tibia with $\frac{1}{2}$ in. lengthening of the right tibia; the right leg below the lower pole of the patella measured 13$\frac{1}{4}$ in.—the left leg 12$\frac{3}{4}$ in. Full range of foot and knee movements; no enlargement of the inguinal glands.

X-rays.—Tibia showed marked sclerosis in its middle third without evidence of sequestration (Figs. 3 and 4). Similar sclerotic changes in the right first metatarsal and the right femur (Figs. 5, 6, 7, 8 and 9). All other bones normal.

Special investigations.—Blood calcium 10 mg./100 c.c. Blood phosphorus 3 mg./100 c.c. Alkaline phosphatase 8 units. Cholesterol 132 mg./100 c.c. W.B.C. 7,100 (polys. 34%, eosinos. 2%, lymphos. 44%). Red cells and platelets normal. E.S.R. 4 mm./1 hour. Widal agglutination test negative. W.R. and G.C.F.T. both negative.

It was decided to do a linear biopsy not only for diagnostic purposes, but to relieve pain. This we regarded as being due to periosteal expansion and interosseous pressure. Accordingly on 27.10.49 a biopsy of the tibia was performed (Figs. 10 and 11). In addition a small portion of the fibula was excised to study the normal bone appearances.

Pathological examination (Professor Dorothy Russell).—The slice of tibia (Fig. 11) showed a rather abrupt transition from the normal pattern of cortex and spongy bone, present throughout the upper 3·5 cm. (*see* left end of Fig. 11), to the remainder of the specimen, in which the definition of the cortex rapidly became blurred through the merging of its deep border into dense pinkish-grey bone without any vestige of cancellous structure. No periosteum was present.

The portion of fibula appeared normal.

FIGS. 1 and 2.—Clinical appearance.

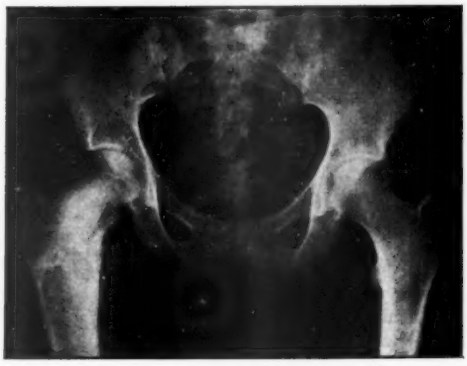


FIG. 9.—A.P. Pelvis.

Microscopic: Blocks from (1) upper end, (2) transitional area, and (3) lower end of the tibial slice, with (4) the portion of fibula, were transferred from formaldehyde to Müller's solution for three months. Decalcification was completed by formic acid and the pieces were then embedded in celloidin. A further block from the lower end of the tibial slice was decalcified and cut on the freezing microtome, the sections being stained with Sudan III for fatty substances.

Tibia: (1) upper end: both cortex and the subjacent trabeculæ appear abnormally thick. In an area near the upper end the hæmatogenous marrow is wholly, in places partly, replaced by cellular fibrous tissue containing a few scattered lymphocytes. Where the replacement is partial this tissue forms a layer over the surfaces of the bone trabeculæ. The fibrocytes have plump oval nuclei and are not clearly distinguishable from the osteoblasts in apposition to the bone. Osteoclasts are scanty in all areas. Osteoid seams, where demonstrable, appear of normal depth. Both in the cortex and in the trabeculæ there are foci of coarse-fibred bone embedded within the fine-fibred lamellar bone.

(2) Transitional area: the more normal bone, as described in (1), changes abruptly with replacement of the cancellous bone by abundant thick anastomosing trabeculæ which enclose cellular fibrous tissue of similar appearance to that seen in the upper part of (1) (Figs. 12 and 13). Osteoid seams are conspicuous and deeper than normal. Osteoclasts are more numerous than in (1). The cortex is greatly thinned: though mostly composed of lamellar bone, there are islands of coarse-fibred bone both here and in the trabeculæ.

No Sudanophil material is present in the soft tissues.

(3) Lower end: the appearances resemble those in (2). The fibro-cellular marrow contains a few small foci of lymphocytes.

(4) *Fibula*: There is no histological abnormality.

Diagnosis.—The appearances are those of a fibrous dysplasia of the bone, with features suggestive both of Paget's osteitis deformans and of osteitis fibrosa. The presence of an island of fibrous marrow towards the upper end of the macroscopically normal segment suggests that the condition may start as scattered foci which subsequently fuse. But further examination might have shown that this apparently discrete area was linked with the main area. The areas of coarse-fibred bone in the thinned cortex indicate a progressive substitution of old by new bone in this situation and explain the outward bowing of the tibia.

FIG. 3.—A.P. Right tibia and fibula.

FIG. 4.—Lat. Right tibia and fibula.

FIG. 5.—Lat. Right femur.

FIG. 6.—A.P. Right femur.

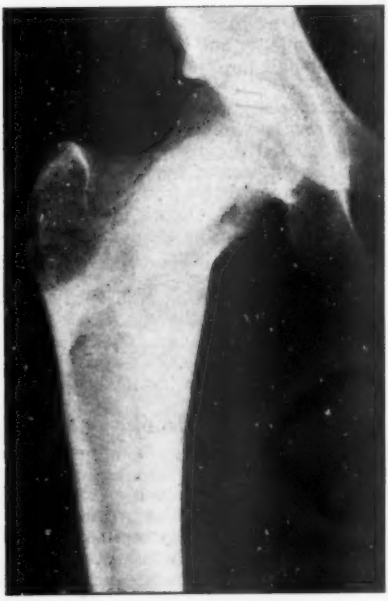


FIG. 7.—A.P. Right hip-joint.

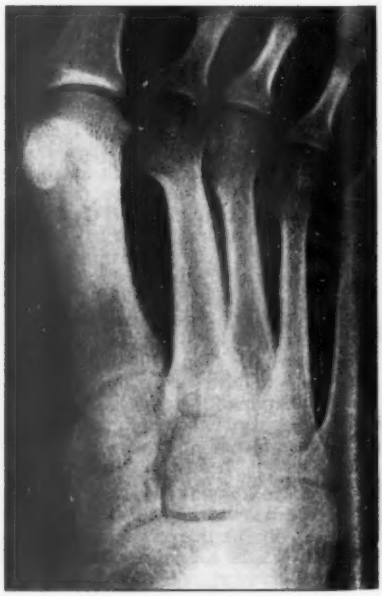


FIG. 8.—A.P. Right metatarsus.

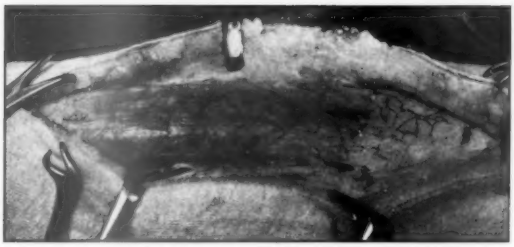


FIG. 10.—Anterior aspect middle third of tibia before incision of periosteum, showing dilated vessels and bowing of bone.

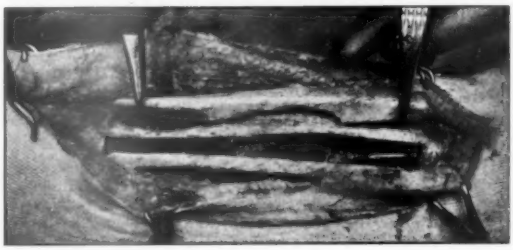


FIG. 11.—Specimen removed for biopsy showing transition from normal bone on the left, to dense sclerotic bone on the right.

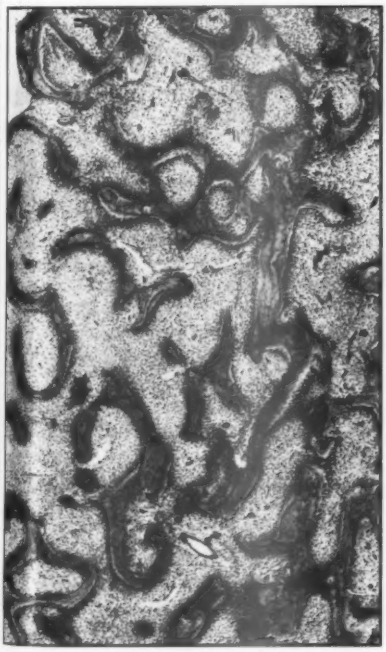


FIG. 12. — Area deep to cortex showing trabeculæ of bone separated by cellular fibrous tissue. H. & E. × 24.

FIG. 13. — As in Fig. 12 showing cells and collagen fibres in a medullary space. Van Gieson. × 360.

The post-operative condition was satisfactory and the wound healed by first intention. She was discharged from hospital on 9.11.49 in a below-knee walking cast.

When last seen on 27.1.50 she had returned to work. She was getting much less pain in the right tibia. Her wound was healed and there was full range of knee and ankle movement.

I wish to acknowledge my debt to Professor Dorothy Russell for her pathological report and for the excellent photomicrographs; also to Mr. R. Ruddick, A.R.P.S., for help in preparing the photographs.

Comment.—The question arises whether this condition is melorheostosis or a fibrous dysplasia in one or other of its manifestations. The balance of opinion at the meeting was in favour of melorheostosis. The girl is otherwise normal, and has no abnormal sexual characteristics. There is also the striking fact that one limb only is involved. The one point of difference between this case and classical melorheostosis is that the sclerosis and density seem rather more central in the case presented.

[*May* 2, 1950]

Symposium on Cerebral Palsy

Dr. Philip Evans (*Department of Child Health, Guy's Hospital*): Cerebral palsy is a convenient name for a group of conditions with differing causes and clinical pictures, arising in early life, due to imperfect development of or damage to the central nervous system above the segmental level. Muscular weakness may be associated with spasticity or flaccidity of the muscles, with ataxia, or with involuntary or inco-ordinate movements.

It may be difficult to recognize in the first year of life. At a slightly later age, the difficulty lies in the diagnosis of the particular type of the disease, for the picture changes with age. Taking for example a single group of known cause, the cases due to kernicterus, we find in the earliest weeks vague signs of cerebral irritation with opisthotonos. This is often followed by a period in which the child appears perfectly well, after which opisthotonos may reappear, this time probably due to muscular dystonia, but by the end of the first year general muscular flaccidity is a common picture. Subsequently inco-ordinate movements, choreic or athetotic, occur and finally dominate the picture, but in mild cases they may not be fully developed until the child is 4 years old.

Age-changes of this degree are common in all types of cerebral palsy and it follows that we may not be able to be dogmatic about the type until the end of the third year. They add to the hazards of diagnosis, which is in any case made hard enough by the imperfection of our methods of examining the nervous system of infants, particularly on the sensory side, and often by ignorance of the neurophysiology of the young.

The incidence of the different neurological types is thus hard to estimate, but it is made more difficult by the selection of cases. For example, 22% of a series of 209 cases seen by me were hemiplegics, while the figure was 53% in a survey carried out by the British Council for the Welfare of Spastics. The latter figure was obtained from education authorities, and is probably too high, for hemiplegics are ambulatory and come to the notice of school medical officers. On the other hand, my figure is too low, for it included patients referred to a special school for children with cerebral palsy who could not be educated elsewhere. Considering hospital and private patients only, my figure for hemiplegics was 38%, but even this may not represent the true incidence, as patients were often referred for particular reasons. Nevertheless, attempts to estimate the incidence in different groups should be made, for to plan the facilities for treatment of all these children simply as cases of cerebral palsy would be to ignore their different needs. In any series, only four major groups are likely to be found to reach double figures in a per cent analysis: hemiplegia, paraplegia, spastic diplegia and athetosis.

Hemiplegia.—The leg improves quickly, so the child goes to an ordinary school. The hand improves little, education is difficult and the child is frustrated. Epilepsy is common and this or its treatment interferes further with education. Intelligence is often mediocre. In many cases the consequent psychological maladjustment prevents satisfactory resocialization, but there is partial success. A hemiplegic newspaper seller is not an uncommon sight. However, some patients adapt very well.

Spastic paraplegia.—Hands, face and speech are unaffected, epilepsy is rare, intelligence is fair, so that socially and educationally the child can succeed, and does not often develop the signs of frustration so common in those who cannot speak or use their hands well. With physiotherapy and transport to school and out-patients department, progress is often good.

Spastic diplegia.—Severe mental defect is common. Even if the child is intelligent the physical handicap is great, and the prognosis poor. In intelligent children, treatment should first be concentrated on speech and handicraft. If it is successful, locomotion should then be encouraged.

Athetoid tetraplegia.—Intelligence is usually adequate, but the muscular inco-ordination responds very slowly to treatment, and often recurs if it is dropped. In the few mild cases it is successful, but in the common severe ones education and treatment are difficult, as grotesque appearance and speech cause maladjustment even in patients who have developed useful degrees of ability.

Intelligence.—I would like to end on a slightly optimistic note. I have been accustomed to think that a child with I.Q. of less than 100 is not likely to improve much. Analysis of the records[1] of a few selected cases in children in a special school shows that the children with low normal intelligence (I.Q. 88) did at least as well as those with intelligence above the average (I.Q. 118). This may not be generally true—although I believe that persistence and desire to improve are worth 10–30 points on the I.Q.—but in these children at least it has been so. This is important, for the bulk of our cases have intelligence quotients below 100.

Dr. C. D. S. Agassiz (*Queen Mary's Hospital for Children, Carshalton*): *Early diagnosis.*—From our experience at Queen Mary's Hospital it is already evident that of first importance in considering the problem of cerebral palsy is the diagnosis in infancy if possible. Cerebral palsy is a condition resulting from a cerebral lesion—it is primarily a neurological lesion—not an orthopædic one. The muscles, initially at any rate, are normal; it is the nervous control that has broken down. Further, as it is a cerebral lesion, the whole musculature is probably involved except in minor lesions. If this is so, then the signs we should look for are those of lack of muscular control, not only of the limbs but of the whole muscular system.

Apart from the history of the pregnancy and labour which may give information of value, there is often a history of asphyxia livida. The mother is usually the first person to notice some abnormality in her baby, and as the whole muscular system is involved, she can usually give evidence of want of development in this system, for example, in such actions as sucking and swallowing. When the infant should have been weaned there may have been difficulty in getting him to take food other than fluids. It is indeed not infrequent to have a child of 2 or more brought to hospital who is still bottle-fed on this account. The child may dribble from the mouth, not because he is an imbecile but from lack of adequate muscular control.

Such infants are often described as "stiff babies". They lie on their backs in cot or pram and make no attempt to view the world around them. If they do make movements of the limbs, they are awkward and slow, or wriggling and inco-ordinated, depending on the type of cerebral palsy. Very often, when they are taken to the doctor, the parents are advised that it is too early as yet to be sure what is the matter and the child should be brought back in a year or so, by which time the evidence of cerebral palsy is much more marked and a diagnosis made—a loss of time in treatment which materially alters the prospect of the extent of recovery.

There are other signs of lack of development of muscular control: perpetuation of various reflex actions long after the time that they should have disappeared, retention of fœtal characteristics such as rounded back, and evidence in the spastic cases of spasticity. The spastic type is the more common and forms 50% of all the cases, a fact of importance as it is probably the easiest to recognize early, and the routine treatment is easier.

It must not be thought that if we look for these departures from normal movement the diagnosis is easy—far from it. Athetosis may be accompanied by tension which may suggest spasticity. The spastic picture may be blurred by irregular movements. The athetoid and ataxic types may present considerable difficulty in differentiation, and so on.

Mental condition.—The second factor of prime importance is the assessment of the mental condition. If the child is to obtain maximum benefit from his treatment it is essential that his mentality should be normal, or potentially normal. If he is mentally retarded as a result of brain damage, or mentally defective, we will not get adequate results from treatment. A child who is unable to move or respond to the ordinary approaches may still be potentially normal mentally. As such infants—and also older children—are so difficult of assessment, we always admit our children for a probationary period of up to three months in order properly to assess their mentality. In the past we have admitted some children who were assessed at their first interview as being eminently treatable but they proved unsuitable, while others who were assessed as unsuitable have proved responsive to treatment. In dealing with older children we do not find that estimates of their intelligence quotient are of much value. It is not easy to take the I.Q. of a child who moves with difficulty and cannot speak. Even when a child is admitted on a probationary period it may take some weeks before an assessment of his mental condition can be made. The intelligent infant will soon show some response to treatment whereas the mentally retarded or mentally defective will show little or none. In making the assessment it is necessary to bear in mind that some of these children are deaf, or deaf to certain tones, and a want of response at first may be due to this deafness; once this is recognized and allowed for, the child responds. Many of the spastic children have

[1] I am much indebted to Dr. John Crosland for allowing me to see and use his records.

squints which may not interfere with their vision materially but certainly some have more serious disturbances of vision which will affect their response to treatment.

Treatment.—The third cardinal principle is that we should know what we are trying to aim at, this is, to provide as far as possible the stimuli which a normal child receives. The normal child as he develops begins to be attracted by objects around him and tries to grasp them, later trying to turn and sit up, and see the world, so receiving stimuli from outside and from within. The cerebral-palsied child is cut off from these stimuli by his inability to move, and though he may develop some movements they are limited and restricted, presumably because the motor paths are insufficiently developed. It is necessary, therefore, that we should try to provide, as far as possible, the stimuli that a normal child receives. It must be borne in mind that no amount of massage is going to have much effect on a normal muscle, no amount of electrical treatment is going to do anything but harm to a spastic muscle. The physiotherapist must be taught how to handle these children, always remembering that she acts only as a guide. The mother, too, should be instructed how to handle the child at home. He has got to learn how to use his muscles himself. In order to develop the motor paths he must receive those stimuli which a normal child receives, and he has to get them repeatedly and almost continuously throughout the day, and not merely at the time of treatment. Once a limited and incorrect motor control has developed as a result of restriction of impressions, external and internal, it becomes difficult to replace that control by one on the right lines, and the longer it has persisted, the more difficult replacement becomes. The occupational therapist and the orderlies must be specially trained in their individual activities for the child's welfare. Only by constant watching will faults be avoided and the child's development speeded. Teachers must similarly be specially trained for these cases.

The mother should be encouraged to carry on the education on suitable lines when the child returns home, or he will retrogress. We find that if a child in our unit has to go away for a time owing to illness retrogression occurs during that period. It is therefore most necessary that when the child is discharged facilities should be provided to continue his education and training.

Appliances: Phelps and others use many mechanical appliances, e.g. calipers, and it may be that in older children there is a place for them. The appliances we use are very simple—skis are practically the only ones apart from simple alterations to furniture to suit the individual child. Our experience with other appliances is small, and it would not be right to express an opinion on their usefulness. But I will make one comment. If the condition is primarily a neurological one I do not understand in what way an appliance like a caliper is going to help. If the muscles are normal it hardly seems desirable to provide a mental picture of an incapacitated leg.

Surgery: If early treatment is given there should be little place for surgery. In older children who have developed contractures or deformities, surgical procedures may be necessary, but if contractures and deformities are allowed to develop in a mentally normal cerebral-palsied child, it suggests that our previous treatment has been a failure. All the more, therefore, should we concentrate on the early diagnosis and treatment of these unfortunate children.

[Dr. Agassiz showed a series of illustrative photographs, *see* Figs. 1–11.]

Miss F. E. Pritchard (*Headmistress, Physically Handicapped School, Willesden*): The Darwinian principle of survival of the fittest prevailed in England in regard to the physically handicapped child until 1893, when for the first time it was made obligatory on School Boards to provide education for the blind and deaf. Epileptics were included in 1899 but it was not until 1921 that any adequate provision was made for the physically handicapped. The first school for physically handicapped children was opened in London in 1900. Willesden opened one in 1909. In 1939 there were 628 Special Schools in England.

The children accepted in such schools suffer from many different types of infirmities. For example, the children at Willesden at present include cases of congenital and rheumatic heart disease, poliomyelitis, cerebral palsy, muscular dystrophy, Still's disease, asthma, and bronchiectasis. These children come from a very wide area in Middlesex and are brought from and taken to their homes every day by coach or car. At present there are 141 boys and girls, aged between 5 and 16, who are looked after by a full-time staff of 10 (Head, 7 teachers, 1 nurse and 1 assistant nurse), and 5 part-time assistants (2 midday assistants, 3 dinner servers). In addition there are four visiting staff—a physiotherapist, a speech therapist, a doctor and an orthopædic specialist. The curriculum is very much the same as in an ordinary school, and gives special attention to the child's individual needs.

How does the spastic child fare in such a school? There are two main points that help and encourage the progress—example and controlled competition. The beneficial effects of good example are of course obvious but unfair competition can have a dire effect on the spastic child. However, competition between individuals and groups having about the same mental and physical capabilities is helpful and is encouraged.

FIG. 1.

FIG. 2.

FIG. 3.

Case 1.—J. H.

FIG. 1.—Intelligent athetoid quadriplegic child on admission, aged 3 years. Note facial expression and helpless condition.

FIG. 2.—Same child three months later. Note carriage of head, closed mouth, abducted legs. He still requires support when sitting.

FIG. 3.—Same child at play. He was asked to suspend activity for the purpose of the photograph. Note good carriage of head, alert expression, widely spaced knees.

FIG. 4.

FIG. 5.

FIG. 6.

Case 2.—V. L.

FIG. 4.—After one year's treatment elsewhere this child still had strabismus, faulty arm posture, and adopts a somewhat typical position of the legs: the head is typically flexed.

This child on admission at the age of 2 years 9 months showed a classically "spastic picture".

FIG. 5.—Same child showing much less marked strabismus, good use of hands and relatively good stance. The tendency to inward rotation of the left thigh in walking remains.

Interval between Figs. 4 and 5 twelve months.

FIG. 6.—Same child during play. Note attitude; improvement in strabismus; good use of hands; wide abduction of the legs; position of head and shoulders. The child was asked to suspend activity for the purpose of the photograph.

FIG. 7.

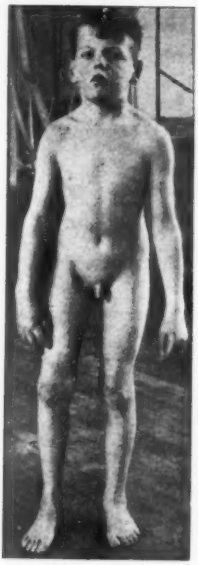


FIG. 8.

Case 3.—R. M.

FIG. 7.—Athetoid quadriplegic boy on admission, aged 10 years 10 months. Note insecure stance, deformed posture of right foot, wayward movements of arms, anxious facial expression.

FIG. 8.—Same child after three months' treatment. In Fig. 7 he is endeavouring to face the camera. In Fig. 8 he easily faced the camera. Note improvements in stance, and absence of anxiety in facial expression.

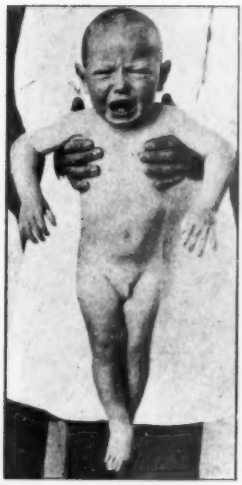


FIG. 9.

FIG. 10.

FIG. 11.

Case 4.—A. K.

FIG. 9.—Child aged 1 year 5 months photographed on admission. Note scissors position of legs: abnormal (fœtal) position of hands: tendency to head flexion.

FIG. 10.—Same child. Note use of hands; abduction of legs; happy facial expression with disappearance of frown lines. (Interval between Figs. 9 and 10 eight months.)

FIG. 11.—Same child kneeling upright for the first time. Note head posture, use of hands, spacing of knees.

The following is an instance of what can be done for the spastic with poor speech. About eighteen months ago a boy and a girl of 5 years were admitted. Both were unable to speak other than baby prattle. The speech therapist, who has only two hours each week at the school, rightly felt that at such a stage she could do very little with them. These children's chairs were placed next to the teacher's desk so that they could see what was going on and hear all that was said between teacher and children. After a short time they were encouraged to join in, and very gradually the voluntary effort to speak and offer information to teacher and to the other children was accomplished. Now they are reading and speaking comparitively well.

The puppet theatre is another way in which the children are encouraged to improve their speech. They model the puppets—which incidentally is good finger exercise for spastics—and they delight afterwards in using them. The child can speak to an audience without being seen and gradually develops confidence in speech. It is a proud day when a boy or girl who has had a long struggle to master reading is able to stand on the hall platform and read to the school. A good way of teaching a spastic child to use a knife and fork is to put him among several other children doing so—and he will soon learn by copying those less handicapped. Children are stimulated to make further efforts when working with children not so severely crippled—they can obtain help from their partners in the class. With this continuous encouragement competition ceases to be a fearsome thing and eventually the spastic comes to take his place in every phase of the school's activity. There are 4 spastics in the football team, and 3 in the swimming class, 2 having obtained certificates.

Working on these lines, it is frequently possible for a physically handicapped child to be transferred to an ordinary school. Between January and December 1949 18 children left for ordinary schools and 6 obtained scholarships, 3 to grammar schools, 1 to a technical and 2 to a commercial school. The future of those who remain till school-leaving age is thought about carefully.

It is not possible with such small numbers to give vocational training even if it were desired —and this a moot point—without at the same time very strictly limiting their choice of occupation. No attempt therefore is made to give them such training but when time comes for a pupil to leave a conference is held at which the child's parents, the Head Teacher, a doctor—and most important of all—the Youth Employment Officer, attend. The pupil and his parents know what type of occupation he would like to take up, the head teacher knows his capabilities, the doctor can advise as to his physical limitations. With this information the Youth Employment Officer can get him placed in industry. Some pupils go for further vocational training, to special training colleges for the disabled. Some get scholarships to technical and other schools. Work in the open market of the shop, factory or office is most desirable and our handicapped children pass happily from the Special Schools to this work.

No scheme of special education for physically handicapped children can be considered complete unless it provides for their guidance during the first few years of their employment. To meet this need an After-Care Committee of seven, including the Head Teacher and Youth Employment Officer, meet twice a term. Five of this Committee visit the old scholars in their homes, until they are 21, to report progress and to give advice and help where necessary.

Mr. K. I. Nissen (*Royal National Orthopædic Hospital*): The operations of orthopædic surgery have a useful but very limited place in the treatment of congenital spastic paralysis. There are several obvious reasons for the prevailing indifferent results of operation. Many primary errors of judgment are made in busy out-patient departments; whether children or adults, the patients behave at their worst away from familiar faces and surroundings, and the surgeon may wrongly decide for or against a line of treatment on a bad display of muscle control. For this reason surgeons who are attached to schools for physically defective children of the type described by Miss Pritchard and who make their decisions after discussion not only with the teacher, the physiotherapist and the parents but with the young patient himself, are much less prone to errors either of commission or of omission.

Many operations on spastic children are performed too early; children below the school age of say 6 years have seldom approached the limit of spontaneous improvement with intelligent guidance along the lines indicated by Dr. Agassiz. For example most of the operations performed for the reduction of spasm in the adductor muscles or the calf could be avoided by a further year or two of patient education. At this tender age operation is too often advised in desperation when a child cannot walk, even round a table; the results can be deplorable. The optimum period for surgical measures lies between late childhood and adolescence, by which time education and physical treatment have had their fair chance and the orthopædic problems have become residual ones certain to cause disability in adult life. Reconstructive measures in adults, unless confined to one limb or at most one side, are seldom rewarding; too often the perseverance and optimism of schooldays have faded.

The actual surgery of spastic paralysis suffers a great deal from unwarranted enthusiasm for techniques used with success in lower motor neurone paralysis. Tendon transplants designed to counter a drop-wrist, an adducted thumb or a pronated forearm depend on a precise cortical control which does not exist in these patients. Perhaps the only transplant of real value is that of the tendon of tibialis anticus from the inner to the outer side of the dorsum of the foot.

Certain operative techniques are losing their former popularity in this country. Neurectomy, either partial or complete, has lost favour, and those who regard the calf muscles as the most important group below the knee have abandoned this operation on the posterior tibial nerve, at any rate in children. Of all such procedures resection of the obturator nerve by the abdominal route, combined with subcutaneous tenotomy of the adductors, is perhaps the most valuable; and this is almost the only remaining use of the tenotome, Little's great surgical weapon, in the treatment of his disease.

Case A.—Brockman's Type of "Gouge" Arthrodesis of the Wrist.

FIG. 1.—The left hand of a young man with spastic monoplegia, showing the maximum degree of voluntary extension of the wrist. The hand is completely useless.

FIG. 6.—To illustrate the function in the same hand (previously useless) four months after operation.

The multiplicity of operative procedures for spastic paralysis can be readily appreciated by reading the appropriate chapter in Campbell and Smith's work (1949), or even better in Bastos' recent monograph (1948). In our personal experience of the correction of residual deformities, by far the best results have been obtained in two common conditions, drop-wrist (treated by Brockman's "gouge" arthrodesis) and talipes equinovarus (treated by Lambrinudi's drop-foot operation and lateral transplant of the tibialis anticus tendon).

With regard to the arm it may be said that any operation near the shoulder is rarely indicated because access to the axilla for its toilet is all that is necessary. Reduction of the biceps power is occasionally required in an adult with an arm like a folded wing; in such rare cases the biceps and brachialis may be divided through a V-Y incision in front of the elbow, leaving the brachioradialis as an adequate flexor of the elbow (McKissock and Nissen, 1950). Pronation of the forearm has received quite an undue amount of attention; such deformity is benign, particularly as the affected hand is generally used for steadying objects, a purpose for which the pronated position is indeed an advantage. Flexion of the wrist approaching a right angle is, however, a great functional and cosmetic disability which can be overcome at the age of 12 or 14 by arthrodesis after simple tenotomy of the main flexors of the wrist (Case A). This operation enables external splintage to be discarded, greatly simplifies the muscular control of the digits, and often restores useful function to a hand previously quite useless. The most difficult problem of all is the thumb which is flexed and adducted across the palm; the operations used with success in anterior poliomyelitis, such as tendon transplants or a massive inter-metacarpal bone graft, are most disappointing.

The equinovarus foot can be regarded as a fairly simple problem of orthopædic surgery. Sometimes all that is required to restore invertor-evertor balance and to improve the power of dorsiflexion is lateral transplantation of the tibialis anticus into the peroneus tertius tendon near its insertion. In most cases, however, Lambrinudi's triple arthrodesis for drop-foot

is required, and a full degree of correction is essential (Case B). If the triple arthrodesis is not followed by lateral transplantation of the tibialis anticus tendon, recurrence of deformity is bound to occur sooner or later, just as it does when the muscle imbalance is due to anterior poliomyelitis or peroneal muscular atrophy.

FIG. 2.—*Case A.*

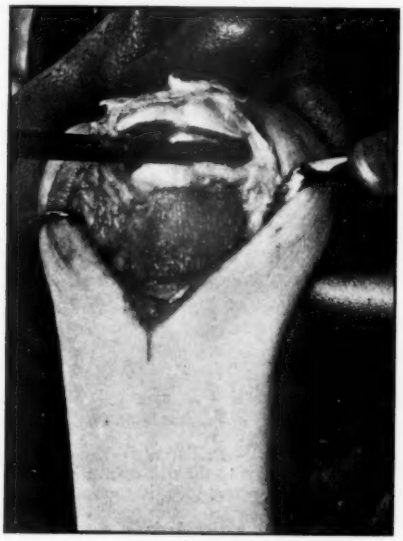


FIG. 3.—*Case A.*

FIG. 2.—Simple division of the tendons of flexor carpi radialis and ulnaris is first performed. Through a mid-line dorsal incision the extensor tendons are reflected to either side, one inch of the distal end of the ulna is resected, and the radius is fashioned into a gouge with a "cutting angle" of some 40 degrees. The proximal row of the carpus and the pronator quadratus muscle can be seen.

FIG. 3.—Using a narrow osteotome held parallel to the dorsum, the scaphoid, semilunar and cuneiform bones are divided, along a plane convex dorsally, into equal anterior and posterior segments. The curved plane of hemi-section of the carpus is carried into the distal row, and especially into the os magnum, almost up to the metacarpal level. A crescent of os magnum can be seen above the end of the osteotome, and more proximally there is the curved surface of cancellous bone of the "gouge" of the radius.

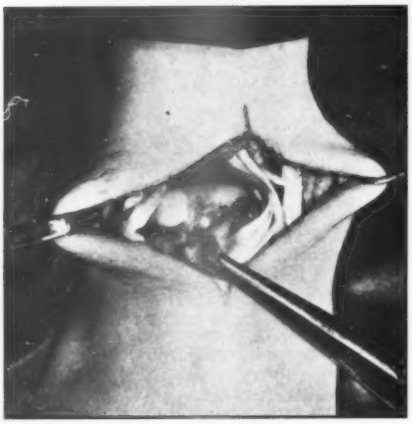
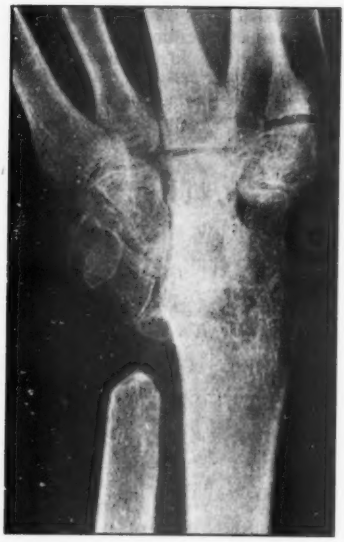


FIG. 4.—*Case A.*

FIG. 4.—The "gouge" of the radius is impacted well into the os magnum, the tendons are replaced, and the shortened incision is sutured. A well-padded full-arm plaster is applied for two weeks, and a scaphoid type of forearm plaster for three to four months, depending on the amount of muscle spasm.



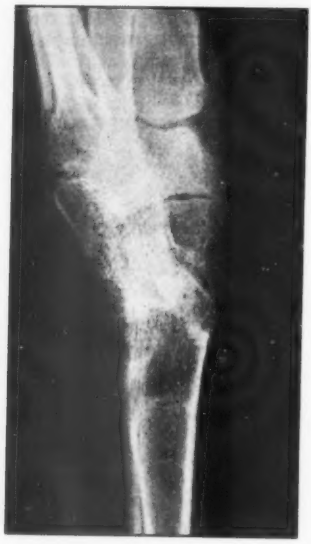


FIG. 5 (*Case A*).—Radiographs showing the final consolidation of the arthrodesis, with complete fusion of the radius to the os magnum. In the antero-posterior view the arthroplasty of the inferior radio-ulnar joint is well seen; in the lateral view some suggestion of the "gouge" of the radius persists.

Case B.—Triple Arthrodesis of the Foot followed by Tendon Transplantation.

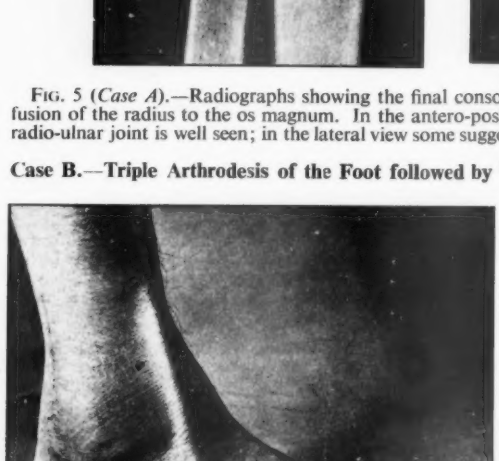


FIG. 1.—*Case B.*

FIG. 2.—*Case B.*

FIG. 1.—The result, after seven years, of Lambrinudi's type of triple arthrodesis, followed by transplantation of the tibialis anticus tendon into the tendon of peroneus tertius, in a case of equinovarus from spastic paralysis. The wear of the shoe is normal.

FIG. 2.—The radiograph in this case shows that the whole head of the astragalus has been resected, that the scaphoid has been placed high up on the neck of the astragalus near the articular cartilage of the ankle-joint, and that there is complete astragalo-scaphoid fusion.

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Section of Urology

President—ALEX. E. ROCHE, F.R.C.S.

[*October* 26, 1950]

Reflections on Nephrectomy [*Abridged*]

PRESIDENT'S ADDRESS

By ALEX. E. ROCHE, F.R.C.S.

WITHOUT a detailed analysis of cases, I shall submit such sporadic thoughts and impressions as have resulted from a consideration of the subject of nephrectomy, including the relatively small number of nephrectomies that have fallen to my lot up to May 1950—namely 213.

So-called painful kidneys.—Those without obvious cause for the pain. The diagnosis of such nephralgia, supposed to be clinched by the doubtful test of reproduction of the usual pain on ascending pyelography, has seemed to me equally doubtful.

I have never purposely performed renal denervation, decapsulation, or sympathectomy for supposedly renal pain with normal pyelograms—in other words, for what, even if the pain is really renal and possibly spasmodic, seems a psychological or nervous condition, perhaps better treated non-operatively, especially since, as in peeling sympathetic fibres from the renal vein, one might inadvertently open it and have to remove a functionally normal kidney. We do not, I think, perform carotid sympathectomy for headache of undiscovered cause, but prefer to use drugs. I do not see why it should be otherwise with the kidney. I do not like to perform operations in order to achieve only psychological benefit. I prefer to send such patients to a physician or psychiatrist.

If surgeons are going to remove various parts merely because these are occasionally painful, they are going to be busy, and there will soon not be much left of their patients.

It seems relevant to mention here the case of a young woman whom I once saw, and whom X-ray films had shown to possess a double pelvis and ureter on each side, but no other urinary tract abnormality—that is to say, no dilatation, infection, stone, or growth; yet nephrectomy had already been done about two years before for apparent renal pain—and it is a fact that such complex kidneys may occasionally be painful, and may even bleed.

This woman was complaining, when I saw her, of recent similar pain on the other side, and it seems to me that nephrectomy was as unsuitable a form of treatment for the first side as it obviously was for the second.

In cases of hydronephrosis, if a plastic operation fails, the second operation is probably a nephrectomy. I have never had to do a secondary nephrectomy for a failed plastic operation of my own for hydronephrosis, although perhaps others may have had to nephrectomize my failures; but I recall doing one secondary nephrectomy after a plastic operation done by another surgeon, and called for because of increasing pain and dilatation. I also well remember assisting a distinguished urologist at a difficult secondary nephrectomy about three weeks after he had done a plastic operation for hydronephrosis. There was pus around and in the kidney, and the patient narrowly survived.

On the other hand, if a plastic operation for hydronephrosis fails, the second operation is not necessarily a nephrectomy. On two occasions I have done a second plastic operation after the symptomatic failure of the first done by other hands, and neither patient has so far come to nephrectomy.

With regard to the textbook risk of renal necrosis after ligature of vessels compressing the upper end of the ureter, which might call for secondary nephrectomy, I have often ligatured radial-sized vessels crossing the pelvi-ureteric junction, but have never had to remove the kidney after this procedure. I suppose that localized aseptic atrophy is the usual sequel.

Nephrolithotomy, with its risk of post-operative hæmorrhage, is listed by Swift Joly as the most serious operation for renal stone, pyelolithotomy being the most benign, with nephrectomy intermediate.

When renal or ureteric stones are single, small, and passable, it may be, as Bacon says in his essay "Of Studies", that "bowling is good for the stone and reins", although I prefer to advise skipping. But, when renal stones are big and multiple, the affected kidney largely destroyed, and the opposite kidney efficient, I think that Bacon would nowadays agree that for such stones bowling is not good, and nephrectomy is better.

I can recall only one secondary nephrectomy needed to stop bleeding after a nephrolithotomy of my own, the second operation being done six days after the first. The patient had suddenly bled through the loin wound, losing about 1½ pints of blood, and becoming shocked and clammy, with a pulse-rate of 150. In one other nephrolithotomy I did immediate nephrectomy, being unable otherwise to control the bleeding, although I suppose that in both these cases, had the kidney been a solitary one, I would have been forced to persevere with less certain means of arresting the bleeding. Both these patients made a good recovery.

Recurrent renal stones after nephrolithotomy may be held usually to call for nephrectomy, the opposite kidney permitting. Still more so might nephrectomy seem to be called for after two previous lithotomies on the same kidney.

However, I recently performed a third right nephrolithotomy on a man of 26, excising the scars of two previous nephrolithotomies by other surgeons, and removing eighteen small stones from the hydronephrosis. My reasons for abstaining from nephrectomy were the patient's youth and the presence of a stone in the neck of the opposite upper renal calyx. Fortunately these reasons were sufficient, as I discovered a third reason only at subsequent left nephrolithotomy, when I found that his left kidney, though not enlarged, was polycystic, the surface being studded with innumerable cysts varying in size from a hemp-seed or smaller to a marble. After operation his blood urea rose to 124 mg.% by the third day, falling to 46 by the ninth day, and, three and a half months later, to 23. He is now well and stoneless, but his future is not too bright.

Polycystic kidney.—Nephrectomy is, of course, but rarely indicated here. Although no nephrectomy for this condition is included in my series, my late chief, L. B. Rawling, removed a typical polycystic kidney from a woman of 25, who had suffered from attacks of left lumbar pain with vomiting, and whose left kidney formed a nodular hard swelling, extending down below the navel. The opposite kidney, felt through a separate incision, was normal in size and outline. Seven years later she had a baby, and later still she wrote to say that her son, aged 3 years, was well, and that she herself had enjoyed perfect health since her operation over ten and a half years previously.

Temple Mursell also records a case of nephrectomy for polycystic kidney. The patient, a coal-miner, had had several attacks of profuse hæmaturia, and had had to abandon work because of lumbar pain. With a post-pyelographic diagnosis of renal neoplasm, Mursell exposed and removed a large polycystic kidney. Over three and a half years later the patient wrote that he was quite well, and working more than ten hours a day. Nearly ten and a half years after nephrectomy he was still well and engaged in active work. Mursell commented: "Perhaps the fact that for ten years the man has never been ill or missed a shift in his mine work is as satisfactory evidence of good renal function as any test to which he could be subjected." Mursell also says: "Had the operation been abandoned when polycystic kidney revealed itself, there can be no question that the patient would have had no prospect but chronic invalidism, and would never again have been fit for work." (*See* Mursell, T., 1929, *Brit. J. Urol.*, **1**, 64; 1935, *Brit. J. Urol.*, **7**, 40.)

Such cases as these show that, given an efficient opposite kidney, with sufficiently urgent symptoms from apparently unilateral polycystic renal disease, there is a definite, if small, place for nephrectomy in its treatment.

Of the various pre-nephrectomy tests of opposite renal efficiency, the intravenous injection of 0·4% indigocarmine, when followed by dark blue effluxes from the ureteric orifice on the side of the kidney to be left behind, has never disappointed me. A good, but less simple, alternative, is a figure of about 2% for the urea content of the urine from that kidney, collected about one and three-quarter hours after the ingestion of 15 grammes of urea by a patient thirsting for six to eight hours. I have also come to rely on good urographic excretion and outlines. But, if in doubt, I prefer the blue test, as being more personal between patient and surgeon.

In spite of the proved efficiency of the remaining kidney, I can recall two or three cases of temporary oliguria after nephrectomy. In one case, that of a doctor's wife, beer and black coffee on the third day apparently worked wonders. In the other case, or it may be two cases, there were, in addition to oliguria, transient renal pain and hæmaturia, the symptoms being thought to be due to temporary renal congestion.

The approach to the kidney.—I have been well served by either the oblique or curved lateral loin muscle-cutting incision, or else a paramedian transperitoneal incision, with a posterior peritoneal cut lateral to the colon.

With the former incision I resected the last rib in one of my first nephrectomies, but have not since needed rib-resection, since manual separation of the wound edges, as Thomson-Walker used to do, with possible dislocation upwards of the last rib, has been enough to gain the needful room.

With the transperitoneal incision, more room can be obtained by extending the incision down towards the pubes; and, on the rare occasions when still more room is needed, by a lateral cut, including the rectus muscle, from the paramedian incision at about the level of the costal margin.

Apart from the rare need for such a lateral extension, converting the incision into a T-shape, one of the advantages of this incision is that no muscle fibres are cut, and another is that the kidney and ureter down to the bladder can be removed at one sitting and through one incision. I know of no other incision which combines these advantages. I have used it, for instance, in a case of renal trauma when it was desirable to inspect other abdominal organs; in cases of large renal neoplasm or hydronephrosis—for example, one hydronephrosis delivered whole, and weighing 8 lb. 4 oz. (3·75 kg.); in a case of papilloma at about the middle of the right ureter, which, obsessed by the patient's obesity and high blood pressure, I had not removed at the time of lumbar nephrectomy for papillomata; and also in two cases of hydronephrosis and megalo-ureter containing stones at the lower end—in the first case, two large stones palpable respectively *per rectum* and *per abdomen*; and in the other, a paravesical packet of eight cherry-sized stones.

The first of these last two specimens was shown to this Section (Nephro-ureterectomy for Large Ureteric Calculi, *Proc. R. Soc. Med.* (1943) **36,** 204), when the criticism was voiced that the incision employed involved a risk to the peritoneum in such septic cases. I believe, however, that, with care, such a risk is more theoretical than practical, especially when one considers what sepsis the peritoneum can successfully deal with in cases of appendicitis; and especially nowadays when many of us operate in the antiseptic shade of chemo-therapeutic umbrellas. In the case of tubercle, however, I should think it wiser to operate extraperitoneally. In the course of lumbar nephrectomy for tubercle I have, while watching operations, twice seen the kidney ruptured in good hands. In these cases of spilling of tuberculous pus the wound broke down and took months to heal.

Although this accident has so far not happened to me, I must confess to a similar accident resulting from an attempt to prevent the very thing that happened. I had divided the renal pedicle in an advanced case of left renal tuberculosis with pyo-ureter, which I had followed down to the pelvic brim, and had here applied two clamps to the ureter. In case the upper clamp should come off, I foolishly (and for the only time in my life) applied a third clamp between the other two, thus rupturing the ureter and spilling pus. I saw this patient some years later. His abdominal wall was distorted with scars and sinuses for which I was responsible.

I have never employed the posterior incision for nephrectomy, since, although it has the advantage of not cutting muscle fibres, it seems to me to suffer from the serious disadvantage of a less adequate exposure than the other incisions mentioned.

I have not tried other and doubtless excellent approaches to the kidney of which one hears much nowadays, and which involve the removal of one or more ribs, and possibly the transpleural route.

In *lumbar nephrectomy*, where the cutting of muscles involves the oozing of blood, I have always left a tube in the wound, except once in a tuberculous case, after a friend had told me that a drainage tube predisposed to sinus formation in tuberculous cases. However, a rise of temperature to 103° F. a few days later led then to the insertion of a tube for a suppurating hæmatoma.

In *transperitoneal nephrectomy*, on the other hand, where no muscle fibres are cut, I have often dispensed with a drainage tube, and never had cause to regret its omission.

Sometimes the kidney may be difficult to find, as I well remember in a case of painful hypoplastic left kidney set in a large mass of perinephric fat in a man of 28.

Intravenous pyelography had shown no left-sided secretion, no urine came from a left ureteric catheter, and this was repeatedly arrested at 11 cm., radio-opaque fluid running down to the bladder, but none upwards.

These facts and the absence of the left half of the sacrum suggested a congenital condition, which was the case, the left kidney being represented by a small flat plaque of cystic kidney-coloured tissue ending below in a solid fibrous cord of about the size of a skin nerve and about four inches (10 cm.) long, which, below, was continuous with the ureter which I had catheterized, and of which I removed the upper half inch (1·25 cm.).

Operative time.—Provided that accuracy is not sacrificed to speed, I have always thought it in the patient's best interests to operate as quickly as possible.

The less anæsthetic and surgical trauma, the less the blood loss, and the sooner the patient is back in bed, the better, and the lower the mortality.

With anæsthesia at their disposal surgeons have lost the incentive, and even the ability, to be speedy, which they had in pre-anæsthetic days. Though pain is abolished, shock remains; and, if one does not normally practise speed when, as with a fit patient, it is not essential, it will not be possible to do so when, as with a very ill patient, speed is vital.

In a recent paper on "Synchronous Combined Total Gastrectomy", the authors thought that the operative time might bear some relation to the mortality (Hume, J. B., and Blackburn, G. (1947) *Brit. med. J.* (ii), 817).

In this series of 213 cases, the time of operation (by which I really mean from first incision to last stitch) was noted in 209 cases. The period varied from twenty-three minutes for multiple stones in a woman of 71, to two hours and twenty-five minutes for a huge hypernephroma in a youth of 18; the average time for the 209 cases was one hour and one minute. I am unable to compete with those who say that they whip out kidneys in ten minutes. I always like to sew up, and that alone takes me about ten minutes.

Operative mortality.—In the present series up to May 1950, the mortality for the last 85 cases was nil. The previous case, however, which I have thought fit to include among the deaths, was a secondary nephrectomy on May 5, 1943, for calculous pyonephrosis in a man of 57. He died on June 7, 1943, the day after cystostomy for old perineal fistulæ and abscesses. This was performed thirty-three days after the nephrectomy.

Going backwards I can add 15 more survivals to the 85 before arriving at another death, that of a postman of 53 years. The memory of this fatal case has been a warning to me. He presented himself with hæmaturia, which was sometimes initial, suggesting that the blood came from the prostate, which was enlarged and seen to ooze. However, I also performed pyelography, both descending and ascending. I considered the ascending pyelograms to be within normal limits—the only time I can recall missing the diagnosis of renal neoplasm from a misreading of the pyelogram. I usually prefer to make my own interpretation of such films, having removed many renal neoplasms where the expert radiological diagnosis was, for example, "normal", "obscured by gas", "calyceal spasm", "polycystic kidney", &c.

However, to return to our postman. Six months later I recognized him in another hospital. He had had no more hæmaturia, but had a lump in the right loin, seemingly too anterior to be renal. However, it was—a hypernephroma; and, assisted by the other surgeon, I took it out transperitoneally. On the whole, I had not thought it renal, and cannot have enquired about chest X-ray films; and the other surgeon, who did think it renal, had omitted this examination; so that, between us, the chest had not been X-rayed. This was another unusual feature of this unfortunate case, for this is the only case of renal neoplasm on which I can recall operating without the routine chest X-ray film. Ten days later he died, and post-mortem examination revealed multiple lung secondaries. It is rare, at the time of proposed nephrectomy for neoplasm, to find radiological evidence of pulmonary secondaries; so that it is indeed a strange and sad coincidence that the only such patient in whose case an X-ray picture of the chest was omitted should have been the very one to have lung secondaries. Among the many lessons of this case is that of a double cause of hæmaturia in the same patient.

Including these 2 cases, I find that there were 13 deaths in the total of 213 cases, representing a mortality of 6·1%; but in the last 100 cases there was only one death, and that, as already stated, over four weeks after nephrectomy and after a subsequent operation on the bladder.

In these days, when there seems to be a certain diffidence in confessing to any operative mortality at all, it is instructive to recall that in 1899 Tuffier's tables gave the mortality of 200 lumbar nephrectomies as 28·4%, and of 161 transperitoneal nephrectomies as 44·1%; while Sir Henry Morris in 1900 reported 95 nephrectomies with 17 deaths.

Apart from one case each of septicæmia with renal carbuncle, and shock with renal, and perhaps suprarenal, trauma, my deaths occurred either in cases of calculous pyonephrosis (including infected hydronephrosis) or else in cases of neoplasm.

The absorption of poisons from a long-standing pyonephrosis weakens the heart. I remember assisting, at St. Peter's Hospital, at a nephrectomy for this condition, the patient dying the same day, and post-mortem examination revealing a streaky myocarditis. In a nephrectomy of my own for pyonephrosis it took about three weeks for the pulse-rate to settle from 130 to normal; and in another case death occurred on the table at the end of the operation.

If, in freeing a large pyonephrosis, its cavity be accidentally opened, and pus pour from it, it is often wise just to insert a tube, leaving the nephrectomy to be done at a second stage, when the advantages of the delay are seen in the smaller size of the mass and in the greatly lessened chance of infecting the peritoneal cavity. One patient, aged 61, with a right-sided, non-calculous, non-tuberculous pyonephrosis, had it thus removed in two stages, the nephrectomy being done three weeks after nephrostomy; and one and a half years later had his prostate removed, also in two stages.

Again, in attempting the removal of an adherent pyonephrosis, if the peritoneal cavity be opened, the hole should, if possible, be immediately closed, lest a thin-walled part of the pyonephrosis should also be penetrated, and pus leak into the peritoneal cavity.

On January 1, 1950, after an interval of twenty-one years, I saw the first patient on whom I performed nephrectomy, on December 10, 1928, at St. Bartholomew's Hospital. It was a secondary right nephrectomy for calculous pyonephrosis. Stones had been previously removed elsewhere, and I had difficulty in persuading the patient that nephrectomy was the right thing to do.

The mortality of nephrectomy for neoplasm is reputed higher than that of nephrectomy for non-neoplastic conditions, and my figures, small as is the total number—three deaths in 31 nephrectomies for neoplasm, or just under 10%—seem to support this view.

Referring to post-nephrectomy survival in cases of renal neoplasm, F. J. F. Barrington (1939, *Clin. J.*, **68**, 6) stated that "most of the patients operated upon are dead or have obvious signs of recurrence within two years". This statement, while seeming unduly pessimistic, contains a large element of truth. Thus, of 5 renal neoplasms removed by me in 1936, one patient died six and three-quarter months later, another after three years, and a third after seven years, from local or general recurrences; a fourth patient developed a secondary deposit in the left great femoral trochanter three and a half years after operation; while the fifth patient, a girl of 6, who had an adeno-carcinoma replacing the lower half of the left kidney, and who has sent me a Christmas card every year since 1936, is the only survivor of the 5.

But I think that that year may given an unfair picture, as many of us, doubtless, have patients alive and well several years, some of them more than ten years, after nephrectomy for neoplasm.

Some well-known textbooks speak of preliminary ligature of the renal vessels as an advantage of transperitoneal nephrectomy for growth, as tending to prevent the manipulative forcing of neoplastic cells into the circulation. It may be that such preliminary ligature is possible with a kidney of about normal size—an exception with neoplasm. But, unless one performs transperitoneal nephrectomy for all renal neoplasms, irrespective of size, it is difficult to see how this advantage will be achieved.

Reserving, as I have so far done, transperitoneal nephrectomy for massive growths, my experience has been that the renal pedicle is the very last thing that I find, so that I can rely only on gentleness to try and prevent metastases.

Of course, if it can be proved that, in the cases of renal neoplasm where kidney enlargement is minimal, and in which therefore preliminary transperitoneal pedicle ligature might be possible—if it can be proved that post-operative secondaries are rarer than after lumbar nephrectomy, then it might follow that lumbar nephrectomy for neoplasm should no longer be done. But I know of no such proof; it would need a large series of cases; and the findings of one large series often conflict with those of another large series. For the present, therefore, I shall continue to reserve transperitoneal nephrectomy for massive growths. In 2 such cases the lower ribs were everted on the side of the mass; I do not remember seeing this sign in non-neoplastic conditions.

Complete nephrectomy usually implies partial ureterectomy, and complete nephro-ureterectomy implies partial cystectomy. Such an operation, probably to be considered only in cases of neoplasm, and especially papillomatosis, of the renal pelvis and ureter, not only repels one from its extensiveness, but has been declared by Macalpine to be harmful. All that is necessary is removal of the kidney and ureter down to the bladder, leaving the intramural part to be dealt with, if necessary, by cystoscopic diathermy. In the case of a fat lady of 68, whose right kidney, and subsequently right ureter, I thus removed for papillomata, no further hæmaturia or bladder papillomata developed during her remaining nine years.

Cases of renal papillomata show that one cannot rely on absence of dilatation of the ureter as proof that distal ureteric papillomata do not exist. I have had cause to regret that, at the time of nephrectomy, I did not remove more of the ureter—for instance, in one man with a fat, muscular, vascular loin, when the theatre temperature, on June 3, 1947, was 93° F. In such cases I should now seriously consider transperitoneal nephro-ureterectomy down to the bladder.

With regard to solitary cysts, I have never, as some do, tried to shell them out entire, any more than I have ever tried to shell out a hydrocele entire, but, analogously with a hydrocele, have usually contented myself with clipping away the wall of the cyst down to the renal edge, and have thus avoided the bleeding of which one hears as sometimes attending the attempt to remove that part of the cyst wall which lies against the kidney, and which it seems to me unnecessary to remove.

On the other hand, when, as with some cysts, hæmaturia has been a prominent feature (hæmaturia due, one may suppose, as in some cases of hydronephrosis, to rupture of

capillaries congested by pressure), and when, even at operation, the possibility of the co-existence of a renal neoplasm could not be excluded, I have performed nephrectomy.

In the case of one such huge cyst of the right upper renal pole in a man of 34, who had twice had port-wine hæmaturia—once eight years previously, and then not again till eight days before being seen—and who had also had an occasional ache in the right loin during the last three years, his doctor, as luck would have it, watched me deliver, through a lumbar incision, and above, and continuous with, the relatively small, though normal-sized, right kidney, a huge tense rounded mass of the appearance and consistency of the right lobe of the liver. The absence of guts, however, cheered me, and, as I was wondering what it was all about, the hæmorrhagic cyst burst with a shower of what looked like chocolate sauce. I think the doctor was duly impressed, but I am not certain in what way; and the patient did very well.

52 nephrectomies for tubercle without a death may be satisfactory, but in several cases post-operative symptoms left much to be desired, increased frequency and hæmaturia persisting, possibly due to the fact that I have never removed the ureter for tubercle below about the level of the pelvic brim at the time of nephrectomy, nor felt called upon subsequently to remove the ureteric stump.

It may be that in some cases results would be better if the ureter were removed down to the bladder. However, what one gains on the swings one may lose on the roundabouts, since the complete routine removal, at one sitting, of kidney and ureter down to the bladder is a more serious procedure than nephro-ureterectomy down to the brim only. Even in the hands of an expert craftsman I recently heard that, I think in 10 such cases of full removal, 3 patients had died from tuberculous meningitis.

In one of my patients, fourteen years after nephrectomy for tubercle, the urine, while persistently free from tubercle bacilli, was infected, and, while the bladder was of good capacity (13 ounces), recent right loin pain led to the discovery of a right hydronephrosis and huge hydro-ureter above a low right ureteric stricture, presumably tuberculous, since a right-sided lymph-gland, removed at the time of lateral uretero-vesical anastomosis, showed tuberculosis. The anastomosis, over a year and a quarter afterwards, has so far been followed by good results as regards symptoms and blood-urea, this being 26 mg.%.

Another patient, nine years after left nephrectomy for tuberculous pyonephrosis at the age of 45, also began to develop right-sided hydronephrosis, perhaps due to the excessive bladder contractions of persistently increased frequency. Unfortunately his subsequent failure to attend hospital for the next two years prevented any attempt at operative relief, for, when he finally appeared, his blood-urea was 330 mg.%.

In cases of marked persisting frequency after nephrectomy for tubercle, uretero-colostomy seems to be gaining in popularity. In such cases, if the ureter is not so dilated as to suggest uretero-vesical anastomosis as an alternative, it may be that grossly increased frequency justifies uretero-colostomy. However, until urologists can achieve a more valvular effect than they claim for their uretero-colostomies, I think it would take a lot of increased frequency to persuade me to undergo this operation for a non-neoplastic condition. I recently saw, for the first time, a fine man of 32 who, nine months after left nephro-ureterectomy for tubercle in 1946, had right uretero-colostomy done for increased frequency. He has no increased frequency now, certainly, but he has recurrent attacks of pyrexia and right loin pain, right hydronephrosis and hydro-ureter, and a blood-urea of 79 mg.%.

Conditions not primarily renal, in which nephrectomy is indicated. I have had only one case of primary carcinoma of the ureter, the patient being a man of 69 with painless hæmaturia.

Cystoscopy was negative, and intravenous pyelography showed dilatation of the left kidney and ureter down to the iliac region, where the outline was narrow and irregular, a finding confirmed by ascending ureterography, which allowed the diagnosis of ureteric neoplasm to be made. On being further questioned, he admitted slight recent aching in the left loin.

On December 9, 1947, I did left lumbar nephrectomy with the ureter down to below the pelvic brim, and well below the firm spindle in the iliac ureter. Examination of the removed specimen showed that, both macro- and micro-scopically, I was well clear of the growth, a papilliferous transitional-celled carcinoma, an inch and a half (3·8 cm.) long, sharply demarcated below.

However, when I saw him on February 9, 1949, fourteen months after operation, although he looked well and weighed a stone more, he had again had occasional hæmaturia during the last five months, and cystoscopy showed fluffy growth on the left side of the bladder. After two cystoscopic diathermies, I did a partial cystectomy on March 29, 1949, a year and a quarter after the nephro-ureterectomy, and removed the left ureteric stump in continuity with the bladder, which showed no growth, including the site of diathermy. The ureter, however, contained the same sort of papilliferous growth as before, infiltrating the muscular wall, with scattered groups of tumour cells in the vessels and adjacent fat.

On January 9, 1950, two years and one month after the first operation, the patient died with paralytic ileus following on a metastasis in the third lumbar vertebra, for the development of which I doubtfully hope that my delay in completing his ureterectomy was not responsible.

Another primarily non-renal condition for which I have removed the kidney was a huge left retroperitoneal sarcoma in a man of 54, with some dilatation of the faint left intravenous pyelogram. There had been no hæmaturia, yet the respiratory mobility of the mass, and a recent left varicocele, seemed to suggest the diagnosis of left renal neoplasm, a diagnosis not dispelled until after the operation, when it was seen that the large mass merely embraced the lower pole of the kidney, which, apart from obstructive dilatation, was normal. Posteriorly the otherwise encapsuled mass had been found to be attached, and had had to be shaved away, necessarily leaving growth behind. The respiratory mobility must have been a rocking movement on this posterior attachment. The patient had deep X-ray therapy, put on two stones in weight, and resumed work as a head gardener, but within five months redeveloped palpable growth at the same site, followed by root-pains and death about one year after operation.

Another primarily non-renal condition for which nephrectomy may be indicated, and, if done, is definitely curative, is uretero-vaginal fistula of the same side, developing after a gynæcological operation in the pelvis, the kidney above the fistula being later found to be slightly dilated. Having previously been content with nephrectomy for this condition, as being quick, easy, and final, I then thought I would try and emulate my friends, and re-implant the ureter into the bladder. This patient, aged 54, had had a hysterectomy for fibroids, followed, ten days later, by laparotomy for intestinal obstruction. I re-implanted her right ureter into the bladder, but unfortunately a stricture developed at the site, and I could pass no instrument up this ureter; so, on December 10, 1934, I removed her obstructed kidney, the patient surviving her four major interventions very well.

In another case of uretero-vaginal fistula, a left-sided one, I failed to find the ureter because of adhesions, and immediately did left nephrectomy. Had this kidney been the patient's only one, I suppose I should have persisted till I did find the ureter, or stopped and waited a month or two, hoping for the adhesions to resolve. However, when the kidney is not a solitary one, one would hesitate to condemn the patient to a month or two more of delay and leakage.

Thus, for uretero-vaginal fistula, although prepared to attempt re-implantation of the ureter into the bladder, I think at present that nephrectomy is more attractive as being an easier operation and the one certain cure.

Nephrectomy during pregnancy.—I have always suggested, if possible, postponing nephrectomy till after parturition.

However, I remember the case of one very large woman who continually poured blood down her right ureter, the urine from which contained pus and *B. coli*, while the left-sided urine contained neither. Apart from a little upper and lower right calyceal dilatation, the pyelograms were normal. Right nephrectomy became necessary to save life, when subcapsular and submucous hæmorrhages were obvious, and microscopy showed active pyelonephritis.

After operation, the patient, whose doctor had accurately diagnosed hæmorrhagic pyelonephritis, confessed to being four months pregnant, her obesity having previously obscured this condition, which proceeded uninterruptedly to full term.

Besides this case, I can recall one other patient in whom nephrectomy was urgent to save life threatened by continued hæmaturia, the blood in this case coming from the left kidney, and pyelograms being normal. The kidney also was normal, except that a walnut-sized cyst was present near the lower pole, the floor of the cyst being curiously trabeculated. Microscopy of this area showed atypical chronic nephritis.

As regards the vexed question of reno-renal reflex, I have had 2 cases, both in women, where this seemed to exist. The one which I regard as the more suggestive was that of a woman of 34 suffering from exclusively left-sided renal pain, who was found to have multiple right renal calculi, the left kidney being stoneless and of normal function. Since right nephrectomy on July 31, 1941, she has had no further abdominal pain.

Post-nephrectomy complications.—I have encountered severe bleeding from the renal pedicle four times. In the first, during a left nephrectomy on August 2, 1933, for infected calculi in a man of 57, I regret to say that, being unable to grasp the pedicle, I packed the wound firmly with a roll of gauze, and sewed up the wound over the gauze. The patient died within a few hours, and I have never repeated the procedure.

Of the other 3 cases of severe pedicle bleeding, 2 were in right hydronephroses, and the third was in a case of ruptured left kidney. I left two clamps on in all three for about three days, removing them in the patient's bed under general anæsthesia. No further bleeding occurred, and all the patients did well.

The ruptured kidney case, operated upon on February 15, 1946, was that of a man of 21, whom I first saw at a distant hospital seven days after the accident. Temperature and pulse- and respiration-rates were normal, urinary output good, and the hæmaturia steadily lessening. I therefore suggested temporization and ntravenous pyelography. Twelve days later I was asked to see him again, his condition having suddenly become very bad. I asked to see the uroselectan films, but these had not been done; so, after having seen good indigocarmine effluxes from the right ureteric orifice, in spite of bladder clots, I explored the left loin, and found a mass of clots, of which I removed a dishful, and the kidney pulped into three or four well-separated adherent pieces. I shelled out the lower pieces,

but the uppermost one was firmly adherent at one spot to the bed in which it was lying. There was room for only one clamp between the kidney and its bed, and that clamp came off, and an arterial spurt hit me in the forehead. I reapplied the clamp, and managed to get a second one on, both being removed sixty-eight and a half hours later. As stated, the patient did well.

Even in the emergency of traumatic bleeding from the kidney, it is essential, before proceeding to nephrectomy, to assure oneself of the efficiency of the opposite kidney. I remember reading about a patient in whom the omission of this precaution, before the removal of a ruptured kidney which had no fellow, was responsible for a most interesting paper on acute uræmia.

Of course, in renal-pedicle bleeding of lesser degree, when it is not necessary to leave a clamp on, it is enough to compress the pedicle with a large swab, or several swabs, against the vertebral column for two or three minutes (and it is amazing how long three minutes can seem under these circumstances).

At the end of that time the bleeding has usually much diminished, and it is easy to remove the gauze cautiously, and grasp the source of bleeding, ligaturing it in the ordinary way.

It was, I think, in a severe case of this sort that a surgeon, visiting St. Peter's Hospital, told us that he had once left behind a packet of 12 swabs. The theatre sister was sure that no single swab was missing, but, in the emergency, was uncertain of the total number of packets of twelve swabs put out.

Although I have occasionally ligatured the renal vessels separately, I have usually, when possible, put three strong clamps on the renal pedicle, cut the kidney away distal to the upper two clamps, and then applied several ligatures of No. 4 catgut round the whole pedicle.

I have but rarely transfixed the pedicle, since, although theoretically attractive as tending to prevent the slipping of a ligature, this practice involves the possibility of vessel puncture.

Bleeding from the inferior vena cava.—As a dresser I was once present when a surgeon wounded this vessel during a right nephrectomy, death resulting in about two days. If one is faced with a difficult nephrectomy, one hopes for a left-sided, rather than a right-sided, one.

I have once put a lateral ligature over a curved forceps applied to the inferior vena cava, when bleeding occurred at the junction of a right lumbar tributary with the main vein, during removal of a renal neoplasm. The exposure was good, and the ligature easy.

Quite recently, and for the first time, I have had occasion to adopt the manœuvre which, in his last lecture at St. Bartholomew's Hospital, I heard Sir Anthony Bowlby state that he had successfully employed in a case of bleeding from the inferior vena cava—namely, leaving a clamp on it for, I think, three days.

In my case (the fatal one in August this year, which occurred subsequently to the series previously decided upon as ending in May) there was some bleeding from the right side of the anterior aspect of the inferior vena cava in a man of 74, while I was separating with the finger adherent fibro-fat during a right nephrectomy for infected calculous pyelonephritis. After due pressure, I applied a ligature over a curved clamp, and then removed the clamp. As bleeding, though much reduced, still continued, I reapplied a clamp, and left it in position. The patient, who had not lost much blood, improved next day enough to eat an egg, but collapsed that night, his pulse becoming imperceptible at the wrist, and died early next morning.

Unfortunately, I thus did not have the clinical chance of testing the efficacy of the hæmostasis by removing the clamp after three days; but fortunately a post-mortem examination was obtained, which proved that no further bleeding from the vena cava had occurred, death being due to heart failure. The heart muscle was soft, and there was marked stenosis at the division of the left coronary artery. Thus the post-mortem examination gave one the melancholy satisfaction of knowing that the patient had not bled again, and had, as one may say, died cured.

Another rare complication more likely with a right than with a left nephrectomy is a duodenal fistula. I have not met with one myself, but have always thought that, if I did, I would adopt, as an alternative to gastro-jejunostomy, Joly's successful manœuvre, which I heard him describe here. He kept the patient lying on the side opposite to the fistula (I think it was a right nephrectomy), and gently plugged the track with paraffin-soaked gauze. The skin was thereby protected, and thus food, tending to run along the inner curve of the duodenum, rather than the outer, was not lost.

Although I have not damaged the duodenum, I have twice damaged the large bowel—once the cæcum, and once the hepatic flexure; at least, those were the probable areas damaged. Again the nephrectomies were right-sided, and both patients did very well.

The first, a man aged 23, operated on on July 7, 1930, had right renal calculi and also what was reported on as a banana-shaped calculus in the right ureter, this stone being of about the length and width of an adult index finger, and extending to the pelvic brim.

Having lifted up the kidney, and easily freed the ureter down to the pelvic brim, I found there a flat dense band tethering the ureter on its inner side. Being unable to free this, I applied two chol-

cystectomy forceps to this band and to the ureter itself below the stone, where the duct felt of normal size, cutting the band as close to the ureter as possible, and applying a ligature over the lower and inner forceps.

During the next few days swelling and œdema appeared behind and above the wound, which discharged pus. At the onset of offensiveness in this, the house surgeon had it tested for stercobilin, which, to my surprise, was present. But the next day, the sixth after operation, there was no need for this test, semi-solid fæces emerging from the lower end of the wound. During the time of fæcal discharge, namely from the sixth to the sixteenth day, the temperature varied daily from 99° to 100° or 101° F., and on one day to 103° F.; but the bowels continued to act naturally, encouraging the hope of spontaneous closure of the fistula, a hope happily realized. The final scar, though wide, showed no bulge on coughing, and the patient has since then had twenty years' good health.

Nine years previously the patient had had an emergency operation for acute appendicitis, no tube being inserted till four days later, when a second operation was performed for an "abscess on the intestine".

From the semi-solid nature of the fæces, and from the fact of their being discharged from the lower end of the wound, it would seem probable that the tough adhesion encountered at the pelvic brim contained a piece of large bowel, most likely cæcum, unnaturally adherent posteriorly as a consequence of the previous operations and suppuration, after which his urinary trouble had begun. Sloughing of the part strangled by the ligature would explain the fæcal discharge after some days.

The other case of bowel damage was even more startling. On May 14, 1946, I had drained a right perinephric abscess, containing 4 or 5 ounces of thick yellow pus, but no tubercle bacilli or other organisms (although there was a poor growth of atypical *B. coli*), in a woman of 23, from whose right functionless kidney, containing many X-ray calcifications, thick yellow pus was later seen issuing into the bladder. *Staphylococcus albus*, but no tubercle bacilli, were found in this pus. Twenty days after drainage I removed the right kidney—a very difficult procedure, the kidney being set as in plaster of Paris. Thinking that I had opened the peritoneal cavity on the inner side, I made to close the gap, after removal of the kidney (which proved microscopically to be tuberculous, with areas of caseation and calcification), only to find, to my horror, that I was looking at the lumen of the gut, opened extraperitoneally. In an attempt to discover which part of the gut it was, I inserted a finger, and found that it could be passed directly inwards, and also distally, in L-shaped fashion. I think it must have been the hepatic flexure. I sewed up the rent with a continuous suture about 1 to 1¼ inches (2·5–3 cm.) long, buried this, and put a tube down it; and was pleased that fæces did not discharge until the sixth day. The discharge ceased to be fæcal in eight days, becoming merely purulent, and finally stopping altogether. Like the other patient, this one, apart from some pyrexia and the discharge, remained well throughout, and ended with a good scar.

In a discussion on some of the accidents of renal surgery reported in the *Transactions* of the Philadelphia Branch of the American Urological Association for 1928, Rathbun says that some of the reported cases of wounds of the large bowel "have been followed by persistent fæcal fistula, many of them requiring secondary operation for closure". In so far as this did not apply to the 2 cases just described, my patients and I were lucky.

Apart from the œdema preceding an intestinal fistula, I can recall 2 cases of wounds puffy with surgical emphysema after renal operations, one of which was a right nephrectomy, and the other, I think, also a nephrectomy. One thought of gas gangrene, but the state of patients and charts obviously excluded this, and the condition seems to have been one of enclosed air and some slow idiosyncrasy in its absorption.

More alarming are cases of pneumothorax, of which I have had several. The first occurred on July 17, 1930, during a very difficult left nephrectomy in a woman of 26, who two years previously was said to have had a pyelitis of pregnancy. She had a small stone wedged in the left renal pelvis, and a huge loculated adherent pyonephrosis.

After patiently freeing this, I finally found that the upper pole was so densely adherent that I could not free it by any justifiable amount of force. So, pulling the kidney down, I applied two pairs of cholecystectomy forceps to the resulting cone of tissue, keeping very close to the kidney, and cut between the two forceps, when the upper one came off, disclosing a half-crown-sized rent in the dome of the diaphragm, through which I could see and touch lung. The kidney, diaphragm, and pleura must have been firmly welded together. I well remember having to kneel on the theatre floor in order to suture the rent with 5 or 6 interrupted sutures.

Next day the patient's respiration-rate was 60 a minute, falling to normal by the third day. It was further interesting that she had clavicular pain, worse on the left than the right. This also soon vanished, and she had another baby within two years.

One case of pneumothorax occurred after a right nephrectomy, on October 22, 1946, for infected calculous hydronephrosis in a man of 32. Post-operative pyrexia and raised pulse- and respiration-rates on the second day led to the physicians being called in, when 1,300 c.c. of air were aspirated from the right side of the chest three days after operation. Temperature and respiration-rates having subsided, and the patient seeming well, and the opposite kidney having, of course, been previously proved efficient, I was amazed to learn, ten days after operation, that the blood-urea was 440 mg.%. The patient's tongue was moist, he had no headache, and his general condition seemed good. However,

there had been relative oliguria, and there were occasional slight twitchings round the mouth, and also slight hiccup. The blood-urea gradually fell to normal in twelve days.

Looking back for a possible explanation of this unique sequence of events, I seem to remember, before applying the ligatures to the renal pedicle, having to brush a few fibres off the tip of my clamp. These fibres may have been diaphragmatic, and air may have been sucked into the pleura at inspiration through a small unperceived hole in diaphragm and pleura during the first day or two after operation. Anyway, since then I have been very careful to see that the tip of my pedicle clamp is quite free. To explain the uræmia, I can only think of a toxic nephritis due to absorption of organisms or poisons from the compressed lung.

Recently looking through my notes, I discovered two other cases of post-nephrectomy pneumothorax.

One was in a youth of 18, whose case has already been mentioned, and who died on the table after removal of the kidney for left calculous pyonephrosis, death being due to cardiac failure from marked toxic degeneration, owing to poisonous absorption from the pyonephrosis.

At the post-mortem examination, which showed very considerable toxic change in the heart, with mottled pallor of its muscle, and dilatation of all its cavities, very dense perinephric adhesions and scar tissue were found to be still present, with penetration of the peritoneum and of the left cupola of the diaphragm, the left lung being almost completely collapsed. Dr. Keith Simpson said that there was no evidence that this had accelerated death in any way.

The other case was that of a man of 55, who had had six operations for renal stone in eight years—two operations on the right side, and four on the left, where he now had a calculous pyonephrosis, and where the site of an old urinary fistula had reopened nine days before a very difficult left nephrectomy, which was but partial, for a few bits of kidney were left adherent to the colon, and, it was thought, a little bit of the upper pole was left behind, the operation being partly extra- and partly intra-capsular.

Eleven days later 300 c.c. of air were aspirated from a left pneumothorax, and, three days later still, a further 800 c.c.

Two weeks later (that is, four weeks after operation), he had improved to the stage of walking, when, having had a little blood-streaked sputum in the last four or five days, he suddenly coughed up half a pint of bright blood, and died almost immediately.

Post-mortem examination showed the left lung to be air-containing and partly re-expanded. A small exostosis was present on the right side of the seventh or eighth thoracic vertebra; and immediately adjacent to this was a small walnut-sized aneurysm, springing from the corresponding intercostal artery just beyond its origin from the aorta. There were adhesions between the aneurysm and the lower lobe of the right lung. Rupture of the aneurysm had occurred, filling the right lung and making it almost solid.

It cannot be a coincidence that 3 of these 4 cases of pneumothorax occurred during removal of a left calculous pyonephrosis.

The remaining case, as already stated, occurred on the right side during the removal of an infected calculous kidney, in the course of which it was thought that a few diaphragmatic fibres, and possibly a small piece of the underlying pleura, had been caught in the clamp.

The predilection of post-nephrectomy pneumothorax for the left side is explicable by the greater protection afforded to the pleura on the right side by the liver.

It is owing to such cases, for instance, as that of rupture of an intercostal aneurysm into a lung that it is difficult to be truthful and yet avoid mortality.

I regret that time does not allow of an adequate analysis of even the present relatively small number of cases.

"Art is long, life is short, and judgment difficult."